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# THE
# DUCTLESS GLANDULAR DISEASES

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FALTA

# THE
# DUCTLESS GLANDULAR DISEASES

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VIENNA

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WITH 101 ILLUSTRATIONS IN THE TEXT

PHILADELPHIA
P. BLAKISTON'S SON & CO.
1012 WALNUT STREET

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# PREFACE

The considerable impetus that has been given to the study of the internal secretion in the last two decades quite justifies the experiment of publishing the diseases of the ductless glands connectedly. The experimental physiology and pathology has been dealt with in exhaustive fashion in the excellent work of *A. Biedl.*

The present volume is concerned with *the clinical aspects of the diseases of the ductless glands.* Of the results of experimental pathology I have set forth only as much as seemed to me necessary for the explanation of the clinical manifestations. For the rest of these results the reader is referred to the work of *Biedl.*

In most of the chapters I have tried to describe the clinical symptomatology on the basis of my own observations, such as I had occasion to make, for the most part, at the first medical clinic in Vienna.

Prof. Dr. *L. von Frankl-Hochwart* and Privat-Docent Dr. *R. Stern* I thank cordially for the revision of the neurological part, Prof. Dr. *Stoerck* for the revision of the pathologico-anatomical part, and the latter also for numerous microscopical preparations. The X-ray examinations, when not especially credited, were by Dr. *G. Schwarz*, director of the Roentgen division of the first medical clinic. I thank Assistant Dr. *S. Bernheim* for aid in the working-through of numerous experimental questions. Finally I am indebted to my publishers, the firm of *Julius Springer*, for their assistance in the fitting-out of the book.

W. FALTA.

VIENNA.

# EDITOR'S PREFACE

The aim and effort of the American editor has been to furnish, not merely a faithful rendering of the German text, but also a rounding out of the subject by the consideration of recent American and English views. To this end he has consulted a wealth of material, comprising some hundreds of references and numerous original articles, from which it is quite apparent that many of the investigators have been concerned with the purely scientific or abstruse, rather than with the clinical aspects of the subject. While consulting the literature the editor could not help but feel that when this has been properly digested and classified, a considerable advance will have been made toward raising the status of the ductless glandular diseases to the level of an exact science.

The American and English views mentioned will be found in the addendum that is at the end of nearly every chapter. If some of these addenda bear a too subjective tinge it is because the editor in his choice of the literature was guided more or less by his personal experience, in which case he may not have done full justice to certain chapters. Care has been taken, in adding the new matter, not to confuse the clear-cut scheme of *Falta*, who so admirably separates the various groups of ductless glandular diseases by well-defined lines. This delimitation of the various groups of ductless glandular diseases at the present time is a most desirable generalization which will enable us to appreciate not only the various parts which the different ductless glands play in the make-up of an individual disease picture, but also to individualize in our diagnosis, even as we are now justified in individualizing, to a certain extent, in the types of Basedow's disease. Granted that we are not as yet prepared for this along the whole line of the ductless glandular diseases, it then becomes our obvious duty to ascertain what symptoms the individual ductless glandular diseases, as expressed or evidenced in different patients, have in common, so that the patients may be classed in their respective groups. Only later will the emphasis of differences between individuals of the same group add pleasure and refinement to the diagnosis, and efficiency to the treatment. This is said with a knowledge of the prevailing tendency of certain foreign schools, chiefly the French, to regard each individual patient's condition as a disease picture *sui generis;* which in truth in one sense it really is, but which for purposes of analysis and ultimate progress we are not as yet justified in regarding as such.

As to the text proper, but very little difficulty has been found. Occasionally when the editor could think of no corresponding English expression, an approximate meaning is given, with the German word in brackets.

"Die Erkrankungen der Blutdrüsen" has been translated "The Ductless Glandular Diseases," as forming a sufficiently comprehensive and universally intelligible title. It is especially, however, to the ductless glands with more or less well-defined internal secretions (endocrine organs) that one author directs his attention, so that bodies such as the spleen, diseases of which are well described in relation with those of the hematopoietic system, and *Luschka's* gland, and the carotid body are not here considered.

"Ausfallerscheinungen" has been variously translated "phenomena" or "manifestations" or "symptoms" due to "lack," "deficiency," "loss," "withdrawal," "absence" and in some cases "falling out." "Überlänge" has been translated "upper length;" "Ünterlänge" "lower length." The first mentioned of these anthropological measurements is taken from the vertex to the symphysis pubis, the second from the symphysis to the heels (according to *A. Saenger*, Ueber Eunuchoidismus, Deutsche Zeitschrift für Nervenheilkunde, Bd. 51, Heft. 5–6, 1914, p. 192).

The author's list of references has been corrected to some extent, and the abbreviations of journals changed to correspond to the standard abbreviations of the U. S. Surgeon General's Catalogue. The index has been revised and enlarged.

The editor's thanks are hereby accorded to Messrs. *P. Blakiston's Son & Co.* for the uniform kindness and courtesy shown him in the preparation of this volume.

MILTON KAYTON MEYERS.

PHILADELPHIA.

# FOREWORD

BY

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When *Addison* first described the syndrome which has ever since borne his name, and proved its dependence upon destructive lesions of the adrenal glands, he broke ground in a new field of medical enquiry of the extent of which neither he nor his contemporaries can have formed any conception.

The ductless glands had long been known to anatomists as structures of wholly obscure functions, and only in quite recent times has any wide knowledge been gained of the important parts which they play in the animal economy.

Indeed some thirty years elapsed after *Addison's* discovery before the next step in advance was achieved by the recognition of the dependence of cretinism and myxedema upon disease of the thyroid gland. Since then facts have accumulated rapidly, yet hardly so rapidly as to keep pace with the hypotheses built upon them.

Nowadays the influences of the glands of internal secretion, in which category are included other organs besides the glands which are classed as ductless, hold a very prominent place in medical thought and investigation. As witness the many discussions which took place in various sections of the 17th International Medical Congress, which met in London in 1913, and in many informal gatherings of its members from all parts of the civilized world.

Pathological investigations have come to the aid of physiological research in the elucidation of the functions of these glands in health, and of clinical medicine in the study of the diseases to which they are liable, and of the symptoms by which these diseases are revealed. There is indeed no department of physiology in which more has been learned from the experiments which Nature herself has carried out.

By the removal of individual glands, and by observation of cases in which they have been destroyed by disease, we have learned what results accrue from withdrawal of their influence, and have even been enabled to discriminate between the individual functions of the parts of such of these organs as are compound structures. For it is a remarkable example of the economy of Nature that in some instances two or more structures yielding internal secretions have been welded together into a single compact organ. Thus the chromaffin medulla of the adrenals is clothed with the functionally distinct cortex; and the pituitary body, small as it is, appears to be even more complex.

That certain morbid states result from loss of function of particular glands of internal secretion is a fact so clearly established as to admit of no two opinions. As regards the thyroid gland, if the effects of its removal left any room for doubt, the striking results of the administration of the gland substance in cases of myxedema and cretinism would remove that doubt. Nor is evidence lacking that such cases of athyroidism are but the extreme examples of series of cases of gradations of thyroid defect which bridge over the gap which separates myxedema from normality. To describe such conditions, of impaired but not abolished function, there have come into use such terms as hypothyroidism and hypopituitarism.

Concerning diseases of another kind, of which exophthalmic goiter may be selected as the type, there is no such unanimity. It is widely held that such conditions present the reverse of the picture, and that they result from overactivity of the gland involved, and excessive production of its secretory products.

Many facts may be adduced in support of this theory, such as the effects of partial removal of the thyroid gland in exophthalmic goiter, and of ligature of its arteries, and the results of administration of thyroid extract in excess. Moreover, there are certain less obvious symptoms which suggest a converse to myxedema. For example the exalted tolerance of carbohydrates, which is a feature of myxedema, as contrasted with the so frequent lowering of tolerance in exophthalmic goiter. Such evidence is fully set forth by *Professor Falta* in this work, for he is a staunch upholder of the view that all the morbid symptoms which result from diseases of the glands of internal secretion, so far as they can be ascribed to their secretory functions, are attributable either to depression or exaltation of the function of the gland concerned.

However, there are some, who are entitled to speak with authority, who are unable to accept this interpretation, and who hold that the maladies so often ascribed to excessive functional activity are rather due to perversion of function, and the production by the gland concerned of an abnormal secretion. Such terms as dysthyroidism and dyspituitarism are used to express this conception.

The arguments adduced in its favor are of several kinds. It must be acknowledged that the administration in excess of the active principle of the thyroid gland, although it brings about exaltation of the metabolic processes in strict contrast to the depression of those processes observed in myxedema, and produces some of the symptoms of exophthalmic goiter, does not reproduce the picture of that disease so exactly as to place its origin in excessive functional activity of the gland beyond all question. Again it is urged that it is difficult to conceive of overfunction as resulting from disease, which might rather be expected to impair the activities to a greater or less extent.

As against this it may be urged that it is equally hard to imagine a perversion of the metabolic changes into new lines, other than those in which the several protein fractions, and even the several carbohydrates, are normally dealt with, stage by stage, by specialized enzymes.

The more the internal secretions are studied the more clearly it is being realized how wide is the field of their activities. We are learning that, in addition to the control of metabolism, or rather in virtue of that control, the endocrine glands exert immense influence upon growth and development; and that their hormonic functions are exercised now in the direction of stimulation, and now in that of restraint. Indeed it is not possible to conceive of a control which is wholly one-sided; the controlling agent must be able to curb as well as to urge on. So we are led to think of inhibiting as well as exciting hormones, if that term may be so perverted from its literal meaning.

In addition to our more exact knowledge, so encouraging in its progress, although as yet so incomplete, of the work of the individual glands, we begin to see evidences of an interaction of the organs of internal secretion, as members of a group of immense influence, a hormonpoietic system. Here we are stepping on to far less firm ground than we have hitherto trodden, and we need to move with caution lest our hypotheses carry us further than our facts warrant. Yet the evidence is at the least highly suggestive. We see how removal of a single gland, by operation or disease, is followed by changes in other glands of the group—changes which are best explained by removal of a wonted stimulus or withdrawal of a regulating control.

Moreover there is evidence as *Claude* and *Gougerot* were the first to point out that the various glands of internal secretion may be attacked simultaneously by a morbid process which is described as pluriglandular sclerosis. Where this is the case the clinical picture presents elements of the several syndromes which result from depression of function of the individual glands of the group. Thus there are suggestions of hyperthyroidism, of pituitary defect, of genital hypoplasia, and of Addison's disease, side by side in the same patient.

The interrelation of the endocrine glands and the nervous system is yet another subject full of interest, and which receives full consideration in *Professor Falta's* pages. How close is the control exerted by the vegetative nervous system over the organs of internal secretion is brought home to us when we consider such phenomena as puncture glycosuria. It may now be taken as proven that the impulse conveyed to the adrenals by the splanchnic nerves excites a temporary excess of secretion of these glands, and to this the excretion of sugar is due. Thus it is suggested that not a few phenomena, attributable to nervous impulses, are produced through the instrumentality of the endocrine glands, and the symptoms referable to disturbances of their functions are not necessarily due to actual disease of these organs. It may be that such is the explanation of much which is still obscure as to the part played by the pancreas in diabetes.

The literature of internal secretions is already a very large one, and in the monumental work of *Biedl* we have set before us all that is known of the subject from the standpoints of physiology and experimental pathology.

The present work has a different scope and aim. In it the maladies of the hormonopoietic system are for the first time discussed in a single volume, and from the clinical standpoint. It will be welcomed by members of the medical profession in all lands, for in it will be found accurate and detailed descriptions of the symptom groups which have their origin in lesions of the glands of internal secretion, and also of some diseases for which such an origin has been suggested.

It is all the more valuable because it is the work of a physician who combines bedside observation with experimental research in the laboratory. *Professor Falta's* important contributions to our knowledge of pathological chemistry are widely known, and he has been led on to the study of the regulators of metabolism by his interest in the chemical processes which it is their function to control.

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# THE DUCTLESS GLANDULAR DISEASES

## CHAPTER I

## GENERAL PART

### Historical Development and Definition

The clinical delimitation of a group of those disease pictures which to-day we designate as diseases of the ductless glands is in part very much older than the conception of the idea of internal secretion as elaborated by experimental pathology. The profound alterations in the development of the human organism after removal of the sexual glands in early life are too remarkable not to have awakened the interest of physicians and the laity as early as the days of antiquity. The breeders of animals had made use of empirical experiences long before the question was discussed as to in which way the sexual glands influence the formation of the body and its distribution of fat. A material progress, however, in the development of the clinical aspects of the disease of the ductless glands began only about the middle of the 19th century. It is associated indissolubly with the name of *Thomas Addison*. *Addison* in 1855, on the ground of pathologico-anatomical findings, referred the sickness that bears his name to a destruction of both suprarenal glands. Then, after *Gull*, *Ord*, and *Charcot* had given the first clinical descriptions of myxedema, *Theodore Kocher* and *Reverdin*, in 1882 and 1883, demonstrated that this disease picture is due to the absence of the functional activities of the thyroid gland. We must regard the year 1886 as a further landmark in the history of the diseases of the ductless glands. In this year *Möbius* first gave utterance to the thought that a disease picture—Basedow's disease—depends on an abnormally *increased* activity of a ductless gland. First in the year 1889 *Brown-Séquard* reported to the Biological Society of Paris concerning experiments that made it seem as though the ductless glands furnished to the blood substances that, when carried by the blood to distant-lying organs, influenced these extensively. *Brown-Séquard* injected juice of the testicle subcutaneously into his own body and observed an increase in corporeal and mental powers that he attributed to the influence of these injections. It is true that *Johannes Müller*, *Ruysch*, and *other authors* preceded *Brown-Séquard;* it was, however, *Brown-Séquard* who first clearly formulated these thoughts, based them on experiments, and thus attracted the general interest of the medical world to them. With the extension of experimental pathology, disease pictures that had formerly been regarded as nervous diseases or constitutional diseases were added to the new disease group in rapid succession. The discovery of pancreatic diabetes by *von Mering* and *Minkowski* placed the pancreas as the central figure in the pathogenesis of diabetes mellitus. Then later came the studies of *Schulze* and *Ssobolew* as to the physiological and pathological independence of the insular apparatus and of *Opie*, *Saltykow*, *Weichselbaum* and *others* as to the histological alterations in the insular apparatus in diabetes mellitus. The very much later discovery by *Blum* of the glycosuric action of the suprarenal extract and the knowledge that "sugar puncture" produces [disruptive] discharge [of the secretion] of the suprarenal through conduction to the chromaffin tissue by way of the sympathetic paths have again brought about partial recognition of neurogenic origin of diabetes as first advocated by *Claude Bernard*. For clinical purposes the chromaffin tissues won recognition through the teaching of *Wiesel*, that hypertonia in contracted kidney originates through hyperplasia of the chromaffin tissue, and through the recognition that in status lymphaticus the chromaffin tissue is ordinarily found to be hypoplastic (*Wiesel*, *Hedinger*). "Thyroid tetany" was discovered experimentally by *Schiff* and clinically by *N. Wein*. The discovery of parathyroprivic tetany by *Gley*, *Vassale*, and *Generali* released, however, the symptoms of tetany from association with those of absence of the thyroid gland and ascribed to the parathyroid gland the decisive rôle in pathogenesis of the individual forms of tetany (*Jeandelize*, *Pineles*, *Erdheim*, *Chvostek*). After *Pierre Marie* had already brought the disease acromegaly, that had been described by him, into relation with the hypophysis, there came gradually into recognition the fact that not, as was originally thought, a diminution but an increase in function of the hypophysis brought about this disease; while in 1901 *A. Fröhlich* and after him especially *v. Frankl-Hochwart* distinguished a disease type, in many respects the antitype of acromegaly, that through the newer investigations of experimental pathology can be regarded as the sequel of a diminution of function of this organ. The pathological anatomy of the hypophysis is especially advanced by *Benda*, who established the adenomatous character of the hyperplasia of the hypophysis in acromegaly, and by the studies of *Erdheim* on squamous epithelioma in hypophysial dystrophy. The histology of the struma of Basedow's disease was thoroughly studied earlier. The pathogenetic place of the thyroid then won further significance through the operative treatment of Basedow's disease (*Rehn*, *Kocher*, and *others*), and through the study of its relationship to sporadic cretinism ("thyreoaplasie" of *Pineles*), to endemic cretinism (*V. Wagner*, *H. & E. Bircher*, *Ewald*, *Scholz*) and to goiter heart (*Fr. Kraus*). Also the significance of the sexual glands for many disease pictures was more exactly studied. Eunuchoidism was sharply delineated by *Tandler* and *Grosz*, and the clinical symptomatology of premature development of the sexual glands was more widely developed. Then were added new investigations as to the relation of the epiphysis [pineal gland] (*Marburg, v. Frankl-Hochwart*) and the suprarenal cortex to premature development; only the thymus gland has not as yet found a secure position in the symptomatology of the disease of the ductless glands. Finally, the symptomatology of multiple ductless glandular sclerosis has been more sharply delimited under the multiform syndrome of "insuffisance pluriglandulaire" described by *Claude* and *Gougerot*, and from it has been separated the disease picture of isolated late eunuchoidism.

These few examples may suffice to furnish an idea of the impetus that the clinical aspects of the disease of the ductless glands have assumed in the last decade. The advance in experimental pathology and especially in physiological chemistry has really not kept pace with this development of clinical pathology and the extension of pathological anatomy. I do not mean to belittle the significance of what has been brought to recognition through experimental pathology; this alone has made possible the rapid advance of the clinical side; I only wish to say that the deficient knowledge of the chemical nature of the active substances given off by the ductless glands constitutes the weak point in the knowledge of the internal secretions and explains why even to-day we are very often compelled to work with hazy ideas. Indeed also in this direction are significant accretions [to our knowledge] present; we can say that through the isolation and chemical definition of adrenalin (*Takamine*) and through the knowledge that this body of relatively simple chemical structure and eminent physiological activity is the specific secretion of the chromaffin system, there has been laid the foundation stone for the physiological chemistry of the internal secretions. Experimental pathology entered here, too, most opportunely, and acted prominently in the discovery of the manifold actions of this substance and its points of attack on the organs affected by the sympathetic nerves. The isolation of adrenalin, it is known, followed from that of iodthyroglobulin (*Baumann, Oswald*). Here, however, are still present slight doubts as to whether we have in this body the specific internal secretion of the thyroid in purest form. Also we are very much less exactly informed as to this body's way of action and points of attack. The knowledge of the specific secretion of the other ductless glands is as yet extremely faulty. Of the suprarenal cortex we only know that it contains cholin, a body of considerable physiologic activity that is distributed otherwise in the organism. That, however, we have in cholin a specific secretion of the suprarenal cortex is improbable. It has been possible recently to obtain from the lobes of the hypophysis extracts of great physiologic importance that have already secured for themselves a place in therapeutics; alone is wanting the chemical definition and the demonstration that these bodies are given off to the blood. All postulates that we must ascribe to a substance in order that we may regard it as the specific secretion of the ductless gland in question have not as yet been fulfilled by any of the hormones. We must ascertain:

1. That the substance in question be found in the efferent blood-path or lymph-path.
2. That after experimental extirpation of the ductless gland in question the symptoms due to the removal are combated by peroral or subcutaneous administration.
3. That through the long-continued administration of this substance manifestations are elicited that are similar to those which clinical evidence leads us to regard as the symptoms following upon increased function, a conception that as the results of the surgical therapy of these conditions has in recent years been made certain.

All these postulates are not fulfilled in the case of adrenalin. Adrenalin has been demonstrated in the blood of the suprarenal vein, but the relationship to clinical medicine is still lacking in clearness. In the case of iodthyroglobulin, the demonstration in the blood or the lymph has been lacking as yet. Hypophysis extract has as yet been studied very much too little, so that we cannot say that it fulfills any of these postulates. As far as other ductless glands are concerned, of which the significance in experimental or clinical pathology is extraordinarily imperfect, as for example the insular apparatus of the pancreas or the parathyroid glands, we have not as yet succeeded in obtaining active extracts, or we are not at all certain that the observed actions of the extracts are specific. The physiological chemistry of the internal secretions is still in its childhood. From it alone, however, is a sharp definition of the disease picture to be expected; the chemical demonstration of the specific substances in the blood even in combined form, the possibility of the demonstration that these substances in lessened, normal, or increased quantities circulate in the blood, would be of great importance for clinical medicine. The biological method in this direction has up to the present failed. Also an important advance in the therapy of the diseases due to lack of these glandular substances in the organism is to be expected from the chemical definition and isolation in pure form of these specific substances. For physiological chemistry the domain of the internal secretions constitutes an inexhaustible field for labor, that theoretically and practically represents a rich reward.

The backwardness of the physiologico-chemical knowledge in this territory explains why it has not been possible up to the present to obtain a clear definition of the idea of internal secretion. According to the original assumption, we understand by internal secretion the giving off of physiologically active substances into the circulation, of substances that through their action on distantly lying organs act in a regulatory manner on the complex processes sustaining life. According to this general definition, however, every tissue in the animal body really yields an internal secretion, as *von Krehl* has already mentioned. The point of emphasis in this definition lies then in the assumption of a chemical correlation of the individual organs of the body in contradistinction to the assumption of a nervous correlation, that formerly was almost all-sufficient. This distinction is indeed not to be maintained rigidly in such a precise form for, as we shall see later on, it must be assumed that to many specific ductless glandular secretions must be ascribed an important and, after its fashion, a quite definite influence on the condition of excitation of the nervous system. We cannot indeed exclude the fact as to whether the action of the ductless glandular secretions does not come about through alterations in the metabolic processes in the various parts of the somatic and vegetative neurones (ganglion-cells, myoneural junctions, etc.). *A. Biedl* happily expresses these changes in our views by the dictum: "Formerly every correlation of organs was regarded as nervous; to-day, however, even nervous actions are regarded as brought about chemically." *Bayliss* and *Starling* have found that under the influence of the acid gastric juice upon the epithelial cells of the intestinal mucosa a substance is secreted by the latter that brings about through the circulation the secretion of pancreatic juice. They call such chemical messengers hormones (from ὁφμάω = I call), a designation that now has found almost general use also as applied to the specific secretions of the ductless glands. With such a general application of the meaning of the internal secretions, not much is to be gained for clinical purposes, as may readily be seen. Also a morphological definition of the ductless glands is not possible, as *Biedl* has pointed out. The histological structure of the individual ductless glands varies according to their genesis from the different germinal layers. Whether the specific secretions of the ductless glands are to be separated from the other hormones through their chemical characteristics cannot be answered at all at the present day. Anatomy, morphology, embryology, experimental physiology, and pathological chemistry do not furnish to-day a satisfactory characterization of the ductless glandular system. Up to the present the demonstration that the individual ductless gland belongs to a system is furnished most distinctly by clinical observation, particularly by the intimate reciprocal relations of the ductless glands under physiological and pathological conditions.

It appears to me therefore that first and foremost it is more important for the clinical point of view not to associate the meaning of internal secretion exclusively with the ductless glands. I might formulate this standpoint in the following way: probably very many cell-complexes of the animal organism possess an internal secretion. *We may designate the totality of all cell-complexes provided with an internal secretion a hormonopoietic system. There are, however, a series of organs the proper function of which we must regard as the production of especially important hormones that are provided with powerful physiological characteristics. It is a common property of these organs that they separate out their specific secretion directly into the blood-path. We therefore call them ductless glands, and their collective total the ductless glandular system.*

The recognition that the ductless glands form a system was of great significance for the clinical aspects of the diseases of the ductless glands. This recognition, that was especially furnished by the serviceable work of *Pineles*, depends not only upon the observations of intimate physiological reciprocal relations, but also upon numerous clinical experiences and pathological-anatomical findings that show that diseases very frequently affect several ductless glands simultaneously, and lead not only to simultaneous increase of function, but also to simultaneous diminution in function, or to a combination of increase of function in some and to diminution of function in others, of these organs.

## Reciprocal Action of the Ductless Glands

I would like here to enter a little more fully into the question of the reciprocal action of the ductless glands; it has become, as *Novak* says, a catch word. An immense amount of work in recent years has been devoted to the study of this reciprocal action, and hypotheses and speculations have grown luxuriantly upon this soil. It is true that up to the present we really know nothing exactly concerning the intimate process in these reciprocal actions, but in a clinical relation such correlations force themselves unmistakably upon the observer; the knowledge of them makes easier the analysis of the often complicated disease picture. Finally, the expressions "reciprocal reinforcement" or "reciprocal inhibition" are in the first place nothing other than circumlocutions for observations. If we view the thing from this standpoint it seems to me that the study of these correlations is fruitful.

For the understanding of these often very complicated processes it seems to me that a separation of **physiological** and **pathological correlations** becomes absolutely necessary. Among *physiological* correlations I mean to include the action that the alteration of function of a ductless gland—diminution or increase of function—exercises upon the function of another otherwise normal ductless gland. These conditions are fulfilled in an ideal manner, when the ductless gland has been extirpated, for example. This can occur in human pathology. I have reference to the total extirpation of the thyroid gland which, formerly, before we knew about the incurable results of the operation, was also undertaken in human beings; or to parathyroprivic tetany after operations on the thyroid gland; or to castration. Further, an inflammatory process may become established in an isolated ductless gland and cause its destruction. In such cases we must by all means be very careful as to the assumption of a pure physiological correlation, as, according to experience, inflammatory processes affect very commonly other members of the ductless glandular system. Here we often find, therefore, as we shall see later, transitions to pathological correlations. Also the increase in function may be produced experimentally in the pure form as, for example, after feeding with thyroid-gland substance. Also in many cases of Basedow's disease and of acromegaly there are no grounds for doubting an increase in function of the ductless gland affected, though even here the transition to pathological correlations is extraordinarily common.

I will now quote some examples of the physiological correlations, confining myself chiefly to the investigations I carried out in collaboration with *Eppinger* and *Rudinger*.

The total extirpation of the thyroid gland with careful avoidance of the parathyroid glands—the electric excitability must show no increase in consequence of the procedure—calls forth a diminution of the total processes of metabolism. Let us examine a little more in detail the carbohydrate metabolism in a thyroidless animal. The power of assimilation for carbohydrates is increased. Now, as it has been known that the capacity of assimilation depends upon the functional breadth of the insular apparatus of the pancreas, we have drawn the conclusion that there must be a relative or an absolute increase of the function of the insular apparatus of the pancreas. But the extirpation of the thyroid gland also diminishes the excitability of the vegetative nerves. For example, the glycosuric action of adrenalin—in addition to other actions, such as the production of a hyperglobulia—is diminished. As it is known that the excitability of the myoneural junction of the sympathetic nerves depends upon the activity of the chromaffin tissue, it may readily be inferred that the activity of this ductless gland (*i.e.*, the chromaffin tissue) is diminished, whether it be that the production of adrenalin is diminished or that the working of this hormone in the organs affected is slighter because of the fact that an otherwise present sensitivization of the organs fails to occur (*Asher* and *Flack*). A sensitivization for adrenalin has also been assumed as due to the extract from the posterior lobe of the hypophysis (*Kepinow*).

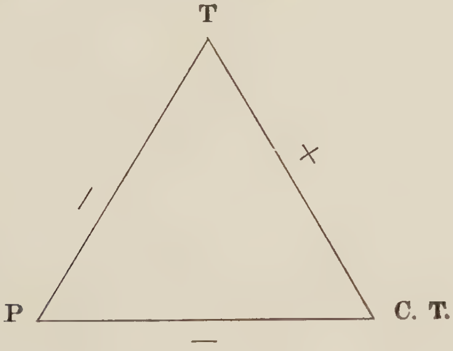

FIG. 1.—P, Insular apparatus of the pancreas; T, thyroid; C.T., chromaffin tissue; —, inhibition; +, reinforcement.

After the total extirpation of the pancreas there occurs an increase of all metabolic processes with a high-grade diminution of the assimilation limits for carbohydrates. In addition there are indications of an increased excitability of the sympathetic nerves (*Löwi's* reaction, increased glycosuric action of adrenalin). Therefore we conclude that there is an increased function of the chromaffin tissue or at least there is an increased action of the circulating adrenalin. In Addison's disease, in which the function of the chromaffin tissue is primarily diminished, we find further a heightening of the assimilation limits for carbohydrates. We explain this as due to withdrawal of the inhibition exercised by the chromaffin tissue on the insular apparatus and to a secondarily increased function of the latter.

*Newburgh, Nobel* and *I* have contributed a further observation. Peroral administration of thyroidin occasions in human diabetes a long-continued hypertonia. We interpret this as the functional increase of the chromaffin tissue in consequence of a heightened sensibility of this tissue or of its central projection fields.

Through this and similar experimental findings and clinical observations the conclusion was drawn as to a reciprocal action between thyroid, insular apparatus of the pancreas, and chromaffin tissue. This is well shown in the accompanying diagram (see Fig. 1).

As before stated, we are not as yet clear as to the intimate process of such physiological correlations. This applies not only to the reinforcement [Förderung] but also to inhibition. We have indeed assumed that increased activity of the insular apparatus inhibits the function of the chromaffin tissue or of the thyroid, and the converse. Another possibility consists in the fact that adrenalin and the pancreas hormone act antagonistically toward each other in the liver; the one in an acceleratory manner, the other in a retarding manner, upon the diastatic processes; or the one acts for the building up of glycogen, the other for its splitting up. Increased activity of the one would therefore disturb the balance between the two ductless glands.[1]

As I have expressed in a recent communication, the relations between thyroid and pancreas seem to me better based and explained in the following way: Increased activity of the thyroid makes greater demand on the function of the insular apparatus. If the insular apparatus does not come up to these demands, the balance between both becomes disturbed. This point of view is supported by a series of clinical observations.

It is futile to raise ideas as to physiological correlation which deal with the question whether one ductless gland can act compensatorily for another. Such an assumption depends upon entirely superficial observation. Every ductless gland has its specific function, although similar features may enter into the sum total of activity. As this point is of important significance, I will quote some examples. The extirpation of the hypophysis, just as that of the thyroid gland, brings about a condition in which the vegetative functions are diminished (*Aschner*). Nevertheless, a dog deprived of its hypophysis looks otherwise than one deprived of its thyroid, as *R. Paltauf* lays stress on. Naturally this is also true in a clinical sense. Practically nobody confuses a typical myxedema with typical hypophysial dystrophy. The extirpation of the parathyroid glands increases the excitability of the vegetative nerves, extirpation of the thyroid diminishes it; the mechanism, however, as I shall show later, is different. It is true that the tetany of the parathyroprivic animal runs a milder course (after associated or subsequent thyroidectomy), because on account of the absence of the secretion of the thyroid gland the excitability of the vegetative nervous system is diminished, but nevertheless the tetany is not thereby prevented.

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[1] Experiments of *Zültizer* and of *Von Bálint and Molnar* point in this direction.

Now, as to the *pathological correlations!* this is furnished by membership in the same system. Diseases which affect one gland often attack very commonly other ductless glands, or a disease process may affect simultaneously several ductless glands, or the entire ductless glandular system. Under pathological correlations I understand the phenomena that symptoms which are furnished through the functional alteration of the ductless glands become concealed, intensified, or otherwise modified, on account of the simultaneous disease of another. This may also be shown experimentally. I have already mentioned that extirpation of the thyroid gland diminishes the excitability of the vegetative nerves, while that of the parathyroid increases it. We observe that the glycosuric action of adrenalin, which is diminished after extirpation of the thyroid gland, is not diminished on simultaneous extirpation of the parathyroid gland and may even be somewhat intensified. Another example: Extirpation of the thyroid gland raises the assimilation limits for carbohydrates and reduces the albumin exchange during fasting. Extirpation of the pancreas reduces the assimilation limits very strongly and increases the albumin exchange during fasting. Simultaneous extirpation of the thyroid gland and pancreas produces indeed a diabetes; this, however, pursues a milder course to the extent that the increase of the albuminous destruction is not so high and the diminution in weight does not progress so rapidly. Therefore, there has occurred a diminution of an otherwise increased metabolism.

Now some examples from human pathology.

Thyroid gland and the anterior lobe of the hypophysis show in many respects much similarity as, for example, in a phylogenetic respect both were formerly glands with external secretion. They show similarity in morphological structure, and in many respects also in their physiological activity. For example, young animals deprived of their thyroid gland or of their hypophysis remain backward in growth, show diminution of the vegetative processes, etc. Often both glands become diseased simultaneously. Indeed, there not rarely develops in acromegaly a Basedow's struma, and in the latter stages occur not rarely, as *Pineles* has described, degenerations of the thyroid gland with manifestations of myxedema. In the cretinic degeneration there is found not rarely, in addition to the goitrous degeneration of the thyroid gland, also such a degeneration of the glandular hypophysis. Finally, in multiple ductless glandular sclerosis, we find that almost always these ductless glands are diseased simultaneously.

Another example concerns the insular apparatus of the pancreas and the thyroid. In typical myxedema the assimilation limit for carbohydrates is raised. Now there are individual cases of myxedema described in the literature in which alimentary glycosuria may be obtained, and even indeed a spontaneous glycosuria may be present on ingestion of diet somewhat richer in carbohydrates than ordinarily. Such cases have been held up to me as irreconcilable with our theory as to the reciprocal actions of the thyroid gland and pancreas. But incorrectly. In such cases it may be assumed that there is a simultaneous affection of the insular apparatus. I have already mentioned that on simultaneous extirpation of the thyroid gland and the pancreas the oppositely directed effect of the absence of the thyroid on the carbohydrate metabolism compensates for the effect of the absence of the pancreas. It is therefore fully comprehensible that in an affection of the insular apparatus disturbances in the carbohydrate metabolism may occur in spite of the myxedema that is present.

Finally, further example is afforded by the pancreas and the suprarenal glands. In the cases of cirrhose bronzée dependent upon severe alcoholism there are found extensive sclerotic processes in the liver, the spleen, and eventually in different other organs, with simultaneous deposition of a pigment that is at first rich in iron and later free of iron (hemosiderosis). With involvement of the pancreas in the sclerotic process not rarely diabetes mellitus comes to pass (diabète bronzée). Now observations have shown that in such cases the diabetes later disappears, as not rarely the cirrhose bronzée involves also the suprarenal glands in the sclerotic processes and may finally even bring about the condition of symptoms resembling Addison's disease; so that we may readily draw the conclusion that the retrogression of the diabetic disturbances of metabolism stand in connection with a more intense sclerosing of the suprarenal glands that occurs later [in the course of the disease].

## Question of Dysfunction

The study of the pathological correlations seems to me to throw light on the question as to whether we are justified in postulating, in addition to an increase in function and a diminution in function of the ductless glands, also a dysfunction. I shall in this book try to explain the individual ductless glandular diseases exclusively as due to quantitative alterations in the ductless glands. I know full well that to-day this opinion is not throughout the generally prevailing one, and I expect to meet with opposition. I believe, however, that I can at least adduce so much evidence for my standpoint that a certain justification for it will not be denied.

As has been previously stated, the physiologico-chemical basis of the hormone teaching is still insufficient. Up to the present only a single hormone, adrenalin, has been defined chemically. A dysfunction of the chromaffin tissue would then signify that a qualitatively altered, faulty, adrenalin is obtained from the chromaffin tissue and given off into the blood path. But every ground for this opinion has, up to the present, been lacking. As a principal argument for dysfunction is adduced the variability of the clinical pictures that may be expressed by the disease of a definite ductless gland. The study of the pathologic correlations teaches us, however, that the pure picture of a functional increase or deficiency may be many times set aside and concealed if other ductless glands become affected at the same time. Thus it not rarely happens that trophoneuroses accompany the diseases of the ductless glands, the combination seeming to me only a loose one. For instance, special stress has been laid on the observation that in the later stages of Basedow's disease sometimes signs of myxedema occur, while the signs of hyperthyrosis are still present. In the description of Basedow's disease I shall dwell at length on these cases, and I believe that in no case is the evidence for the existence of a myxedema absolutely convincing. In common with *Newburgh* and *Nobel*, I have further shown as concerns this question that the great multiplicity of syndromes in conditions of functional increase of a definite ductless gland are for the most part to be explained through diversities of constitution. We have attempted to justify this experimentally. The individual hormones or ductless glandular extracts have very different kinds of action throughout. As I shall come to speak of adrenalin in this connection later, I shall choose as example at this place the thyroid-gland substance. By peroral administration of large amounts of thyroid-gland substance, we can see the following symptoms make their appearance:

1. Tachycardia.
2. Great depression in the blood pressure from center to the periphery.
3. Increase of the fundamental exchange.
4. Increase of the albumin exchange.
5. Increase of the elimination of salts.
6. Lowering of the assimilation limits for carbohydrates, and finally spontaneous glycosuria.
7. Sweats.
8. Mononucleosis.
9. Tremor.
10. Diarrheas.
11. Psychic agitation, etc., etc.

Thus there are produced almost all the symptoms of a Basedow's disease. We almost never, however, succeed in obtaining all these symptoms in a single individual, but we see regularly tachycardia appearing as the cardinal symptom. To this other symptoms group themselves to form definite syndromes; for example, tachycardia, sweats, mononucleosis, or tachycardia, mononucleosis, tremor, etc. We can therefore obtain in miniature almost all the syndromes that we find in cases of Basedow's disease. As thyroidin is always the same, the cause of this dissociation must be ascribed only to the various constitutions of the persons tested. The question as to why this is so in the individual case is naturally hard to answer, as the sum of the partial constitutions (to use an expression of *Martius's*) that go to make the total constitution is enormous. In many respects it seems most reasonable in experimental hyperthyroidism to seek the explanation in the different reaction activities of the ductless glandular system. When, for example, we see that administration of thyroid substance produces glycosuria in one individual, and in another does not alter the carbohydrate metabolism, it may be readily inferred that, on account of the known physiological correlation between thyroid and pancreas, in the first case the insular apparatus has not kept pace with the demands that the hyperthyroidism has made upon it, while in the other case the functional capacity of the pancreas is sufficient. In other cases entirely different constitutional factors appear more strongly in the foreground. For example, in neuropathic predisposition, the symptoms on the part of the nervous system and the mind occur more markedly and have other features. This, ceteris paribus, holds just as good for the [diseases due to] functional increases as [for those due to] deficiencies.

Our standpoint as to dysfunction is important not only theoretically but practically. If we discard dysfunction, the therapeutic indications are much clearer. The results of substitution therapy are thus readily made intelligible, and the operative treatment of conditions due to hyperfunction properly receives its justification only in this way. It appears to me that the study of the pathologic correlations is important for the explanation of many a therapeutic failure. In symptoms due to lack of a gland, a complete result as the consequence of substitution therapy is not to be expected when other parts of the ductless glandular system are involved at the same time. Perhaps in such cases more can be achieved through combined organotherapy. Pertinent contributions in the French literature appear to me to be in part very optimistic. A similar consideration of the pathological correlations is perhaps due in the position of the indications for the operative treatment of the hyperfunctional disease. One would perhaps take exception to a resection of the thyroid when at the same time other manifestations are present that point to exhaustion of another ductless gland, for instance, the chromaffin tissue. In this connection still another factor is important, namely, the relations between the ductless glandular system and the central nervous system. I shall speak about this subject later.

Only a few words yet as to the *intoxication theory* that plays so great a rôle in the study of the internal secretions. The expression "poisoning" is, according to my opinion, well adapted in many diseases due to hyperfunction;

for example, in Basedow's disease. On this account we do not need to assume a dysfunction, as a normal secretion, too, given in excess to the body, may poison it. A fitting example is furnished by adrenalin poisoning. On the contrary, I must assume that no sufficient experimental evidence is at hand for the detoxication theory of the disease due to lack of secretions; that is, for the assumption that poisons normally formed in the organism are *rendered nonpoisonous* in the ductless glands, and that they poison the body when the ductless glands are insufficient. Even the pathogenesis of tetany may be explained without the aid of detoxication theory, as we shall see in the chapter on the subject.

The great number of works as to the physiology and pathology of the ductless glandular system that have appeared in the last decade show the growing interest that physiologists and clinicians take in this subject. What makes the subject so fascinating is the fact that it allows us to have what up to the present was a scarcely anticipated look into the complicated regulatory mechanism of the animal organism. In many respects this influence is especially true for the influencing of the growth and of the metabolic processes. But also the development and the activity of the hematopoietic apparatus stand under the control of this ductless glandular system; finally, the most intimate relations exist between the ductless glandular system and the nervous system, whereby practically all the somatic and vegetative functions, yes even the mind itself, are brought within the zone of influence. To describe in detail this invasive activity of the ductless glandular system into all the vital processes does not lie within the limits of the task I have set for myself. I shall only sketch a few points in gross.

## Influence of the Ductless Glands on the Growth

I begin with the influence of the ductless glands upon the *growth* and the configuration of the body. This influence is apparent and has long been known in eunuchs and through the experience of breeders of animals, although exact experimental work in this direction dates only from recent years. It seems to me most suitable for our purposes to select certain better studied types and to sketch them. [illegible]

1. Loss of the *sexual glands* at an early age or high-grade hyperplasia of these leads to tall growth; the skeleton is built slenderly and shows characteristic proportions (large lower length, large span width, small head). There is found herewith a characteristic distribution of fat and faulty development of the secondary sexual characters. The closure of the epiphysial junctures, and especially of those which under physiological conditions close the latest, are markedly delayed. This is the foundation of the characteristic proportions and the cause of the tall growth. (The assumption of secondary increase in function of the hypophysis, as I shall treat in Chapter

X, I do not regard as warranted.) We may therefore assume that there is exercised by the sexual glands, especially at the time of puberty, an influence upon the zone of ossification in the sense of a definite bone formation. This influence is exercised on the part of the interstitial glands.

2. Absence or high-grade diminution of the function of the *thyroid gland* at an early age leads to dwarf growth; that is, to inhibition of growth. The skeleton retains in general the childish dimensions. The epiphysial closure is to a marked degree delayed. The fontanelles remain open for a long time, the root of the nose is drawn in, the development of the bone-nuclei is very much retarded. The bones already formed show a slight degree of sclerosis. The bones are thick. In youthful individuals with Graves' disease there is found on the contrary a slightly accelerated growth in the length, and a somewhat premature closure of the epiphyses. The eunuchoid distribution of fat is absent. The genitals remain backward in development but not so markedly as in eunuchoidism. Under the influence of the insufficiency of the thyroid gland the endochondral and periosteal ossifications are to a slight degree retarded.

3. Absence of the *hypophysis* in early years also leads, as clinical and recently, also, experimental observations show, to an inhibition of growth. Closure of epiphysial junctures and development of the bone-nuclei are likewise delayed, perhaps not so markedly as in the thyrogenic inhibition of growth, although this is hard to decide, at least in the clinical observations, as the observations on the disturbances do not seem to deal with cases at such an early age. The hypoplasia of the genitalia and especially of the interstitial glands is very much more marked, also when the disturbance sets in later. Correspondingly there is found a eunuchoidal distribution of fat, and even an (secondary) influencing of the body proportions which approximate more or less closely the eunuchoid type.

In cases of youthful acromegaly the relations are very much more complex. The typical cases appear to me, as I shall treat of in greater length in Chapter VI, to be those with a marked accentuation of the functions of the interstitial glands. We find then premature closure of the epiphysial junctures, more emphatic pronunciation of the secondary sexual characters, and premature thickening of the bones with exostosis formation and thickening of the soft parts. In other cases are found, however, inhibition of development in the genital sphere, together with a marked eunuchoidal tendency in the proportioning, with tall growth.

4. In disorders of hyperfunction of the sexual glands, the suprarenal cortex, or the epiphysis in youthful life, we find *premature development* of the whole body, accelerated growth with potentized childish dimensions, premature development of the genitalia and then later premature epiphysial closure, in short a transitory gigantism. Whether these vegetative disturbances can be the direct outcome of those of the organs mentioned, or whether they are

always dependent on a primary or secondary increase in function of the suprarenal cortex, is as yet uncertain.

As to the influence of the other ductless glands on the growth and conformation of the body as yet little that is reliable is known. I shall only mention that extirpation of the thymus glands leads to an inhibition of growth, that is later compensated. I shall treat of this further in the appropriate chapter.

The manner and means in which the ductless glands affect the growth is only partly known. It may be said with certainty that the closure of the epiphyses and hence a definite cessation in the normal growth occurs under the influence of the sexual glands and indeed the interstitial glands; further that the development of the bone-nuclei and the growth in length of the bones is strongly influenced by the thyroid gland and the hypophysis. I would ascribe to the thyroid in this connection an influence at least as great as that of the pituitary. The influence of the latter seems to be very much overestimated, to the extent that the hypophysis has been regarded as the dominating growth center. The disturbances in growth produced by the thyroid differ importantly from those produced by the hypophysis; I would especially attach importance to the fact that in the thyroidal growth disturbances the bones are thick [German word "plump" = coarse, thick, awkward]; in the hypophysoprivic they are slender; the contrary may be seen in the increase of function of these glands in early youth. In youthful Basedow's patients the bones are slender; in youthful acromegalics they are thick and provided with exostoses, and, so far as the disease is not complicated with associated eunuchoidism, the bony processes are thickened. For the overestimation of the significance of the hypophysis for the growth in length the *Brissaud-Meige's* formula for gigantism should be held responsible. According to this formula, gigantism is nothing other than an acromegaly of youth. It seems to me, however, that in gigantism, at least in the earlier stages, there is found mostly a hyperplasia also of other ductless glands, perhaps of the whole ductless glandular system; and especially the suprarenal cortex is often hyperplastic and, according to recent investigations, may influence in many ways the clinical picture of gigantism as well as of acromegaly. I have previously mentioned that also premature development can be associated with an increase of function in this organ, perhaps is regularly associated with it.

Although here too very little is as yet known and explained in a satisfactory manner as to the influence on the growth and bodily conformation through the ductless glands, yet this influence is so striking that it may be concluded that a harmonious development of the body is not possible without orderly functioning of the ductless glandular system. We as yet know nothing as to the intimate processes in this kind of hormone action. Trophic influencing of the nervous system may come into play in many of these actions, as the symmetry in such formative influences seems to signify. Further a specific influencing of the metabolic processes, for example in an athyrosis, is to be thought of; further a modeling influence on the skeleton through alteration of the muscle tonus, etc., etc. It would, however, be a mistake to bring into relationship with the ductless glandular system all variations and diminutions or increases in the growth energy of the protoplasm.

## Influence of the Ductless Glands on the Regulation of Metabolism

The ductless glands assume a still more considerable influence in the *regulation of metabolism.* I shall here choose only a few of the most marked examples. First let us consider the *carbohydrate metabolism.* The pancreatic insular apparatus governs the carbohydrate assimilation, for after extirpation of the pancreas the glycogen formation in the liver and also otherwise in the tissues, especially the muscles, is markedly disturbed. That this consists chiefly in a disturbance of glycogenesis seems to arise from the fact that on low-grade insufficiency of the pancreas the disturbances first become manifest only on alimentary overloading, while otherwise the regulation of the carbohydrate metabolism is proceeding normally. Then an increased sugar-production occurs first in the high grades of the disturbance, for now there occurs also on fasting—hence, with full exclusion of the alimentary influence—hyperglycemia and glycosuria.

On the other hand, the mobilization of glycogen seems to stand chiefly under the influence of the chromaffin tissue, for artificially induced hyperadrenalinemia (through subcutaneous injection of adrenalin or through sugar puncture) brings about a rapid melting down of the glycogen present in the liver and muscles, and perhaps also an increased combustion of sugar, as after injection of adrenalin we saw a rise of the respiratory quotient. Thereby occurs hyperglycemia and eventually glycosuria; after extirpation of the suprarenals or in Addison's disease there exists on the contrary hypoglycemia.

Both these ductless glands are to be regarded as most important regulators of the carbohydrate metabolisn, and we must add to them as a regulator the thyroid gland; for, as previously mentioned, in typical myxedema the assimilation limits are raised, and in Basedow's disease or in artificial thyroidism they are not rarely reduced, indeed spontaneous glycosuria sometimes occurs. As I here again emphasize, the thyroid gland seems to influence especially the pancreatic insular apparatus or the hormone produced by it, as here the alimentary factor is so prominent. A similar regulator influence, although probably not such a strong one, seems to proceed from the hypophysis; I shall speak of this in the appropriate chapter.

So far as the *albumin metabolism* is concerned, we have known for long that the thyroid gland influences it enormously. In Basedow's disease the albumin requirements are increased; the patient must ingest more albumin if he does not wish to use up the albuminous constituents of his body. In myxedema the albumin requirements are abnormally low. In hypophysial and suprarenal diseases these disturbances in the albumin economy are not so distinctly prominent. Also the severe diabetic ordinarily has no heightened albumin requirements.[1]

From these examples it will be seen that the regulatory influence of individual ductless glands on the different metabolic processes is to a great extent specific. While pancreas and chromaffin tissue govern the carbohydrate metabolism, the thyroid gland is especially important for the albumin metabolism. For the calcium metabolism the function of the parathyroid would seem to be of especial importance, as in tetany the assimilation of calcium in the nervous system seems to be disturbed, although also other ductless glands would seem to take a part in the regulation of calcium metabolism. Thus the thymus gland seems to be of importance for the assimilation of calcium in young bones. Administration of thyroid-gland substance or of extracts of the posterior lobe of the hypophysis increases chiefly the elimination of calcium; adrenalin that of potassium and sodium, while the elimination of calcium is restricted. The significance of these experiments for clinical medicine is not as yet clear.

The influence of ductless glands on the *purin metabolism* has as yet been investigated but little. The observation that in acromegaly the endogenous factor of the uric-acid elimination is raised, that in hypophysial dystrophy it may lie strikingly low, and that also the exogenous factor may show oppositely directed alterations, and further that alterations of purin metabolism also occur in the thyroid-gland diseases, as I shall show in Chapter II, makes probable the regulatory influences of the ductless glands on the purin metabolism. I must not off-hand make any statement as to whether the problem of gout will be elucidated by such investigation.

The study of the *respiratory gaseous exchange* has furnished a deep insight into the regulation of metabolism in the ductless glandular diseases. Here also I will limit myself to certain important facts. In Basedow's disease the fundamental exchange is increased. In thyroprivic or spontaneous myxedema the fundamental exchange and the caloric requirements are reduced. In acromegaly a distinct rise of the fundamental exchange is present only when symptoms of Basedow's disease are present at the same time. In hypophysial dystrophy the fundamental exchange is reduced only in especially severe cases. In failure of the sexual glands the reduction of the fundamental exchange is still a moot question and if present is but slight. Investigations of the metabolism in premature development as the results of suprarenal cortical, sexual glandular, and epiphysial tumors have not as yet been made. In severe diabetes mellitus, as will be told about in detail in Chapter XIII, the caloric production in the rest-fasting experiments is not essentially increased, the caloric and oxygen requirements are increased, correspondingly to the loss of sugar and of ketone bodies. According to the investigations up to the present, a considerable influence on the fundamental exchange is to be attributed only to the thyroid gland. It seems to me, however, that for a correct appreciation of the influence that the ductless glands exercise on the metabolic processes and nutritional conditions, it is just as important that we consider the endogenous factors as well as the exogenous factors. By fundamental exchange we mean, as is known, the amount of the carbonic-acid production and of the oxygen requirements, or of the heat production, on ruling out of digestion and muscular work. If we calculate the fundamental exchange per kilogram of body weight, we find in (grown) small and thin individuals higher values than in (grown) large and fat individuals. In youthful individuals the fundamental exchange is relatively larger than in adults. In the small individuals the variations to which it is subject are ordinarily only very slight. The fundamental exchange is a measure for the work that in a resting fasting organism is performed by the heart, the glands, the nervous system, etc., including that which is furnished by a certain muscular tonus that cannot be excluded. That the thyroid enormously influences the fundamental exchange may be readily understood when we consider that in Basedow's disease the organs are in a condition of marked excitement, while in myxedema the vegetative functions are markedly reduced. A certain influencing of the fundamental exchange is to be expected also on the part of the other ductless glands as they too influence the vegetative nervous system in manifold ways, so far as its condition of irritability is concerned, even if their influence does not cause such distinct effects. But also the exogenous factor of the exchange is influenced by the ductless glands more or less pronouncedly. I have reference to the unrest and mental irritability of Basedow's disease, or the apathy and lack of interest of the myxedemic. In tetany we find in addition to the increase in the vegetative functions also an extraordinary influencing of the exogenous factors through the fibrillary twitchings and through the spasms. Also as far as the sexual glands are concerned does an exogenous factor come into play; for instance, in eunuchs there is absent the stimulus to motion and the animation of the normal man. All these are factors that are of great importance for the regulation of the total exchange and for the condition of nutrition.

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[1] Also qualitative alterations of the albumin metabolism are observed in ductless glandular diseases; in tetany, for example, there is a heightening of the ammonia, amino-acid, and polypeptid fractions.

Even more significant appears to me the following circumstance That a normal grown man retains the same bodily weight for years depends on a correct relation between assimilation and dissimilation assured by such different factors as appetite, impulse for movements, etc. On these processes the ductless glands have a considerable influence. We can with great probability, as we shall see later, divide the hormones into anabolic and catabolic (retarding and acceleratory, or assimilatory and dissimilatory). An important anabolic hormone is, for example, the pancreas hormone, as it is very important for the carbohydrate assimilation and, as I am inclined to assume, also for the fat assimilation. This also makes comprehensible an influence of the ductless glandular system upon the regulation of the total exchange (not the caloric production alone). A fattening,[1] that is, a significant increase in the assimilatory processes, would only then be possible when the ability for it, that is, a certain breadth of function of the ductless glands in question, is present, otherwise the organism would protect itself against the increased supply of food. This seems to throw some light on the obesity associated so commonly with certain ductless glandular diseases. The consideration of the fundamental exchange alone would not carry us to the goal, for it is very well conceivable that the fine mechanism of regulation between assimilation and dissimilation is disturbed, without that the activity of the vegetative organs is so much altered that it would come to expression in the fundamental exchange. Only in diseases in which the diminution of the fundamental exchange is quite clear, for instance in myxedema, must, if obesity is to develop, also a disturbance in the relation between assimilation and dissimilation be added, as otherwise the ingestion of nutrition would simply diminish with the lessened need.

Also in those ductless glandular diseases that according to experience are associated with emaciation must there be present a similar disturbance of the mechanism of regulation, although in the opposite direction. The increase in the fundamental exchange in Basedow's disease can otherwise be vitiated by corresponding increased ingestion of food. Here indeed are the relations very much more complicated, as the ingestion of much food may be made difficult through vomiting or through diarrhea. It seems to me, however, that this explanation is not sufficient for all cases. We sometimes see indeed in this very Basedow's disease a paradoxical relation; after initial wasting can, in spite of the persistence of Basedow's disease, an obesity develop, and some have seen in this obesity evidence for a dysfunction of the thyroid gland.

It seems to me very likely that in such cases, in spite of persistence of an increased dissimilation, the assimilatory processes win the upper hand on account of a gradual developing hyperfunction of the pancreas. On the other hand, emaciation may enter in on account of primary disturbance of assimilation, as is the case in severe diabetes mellitus; here the gross exchange is increased, the production of calories not however increasing.

Finally there must be ascribed to the ductless glandular system an influence on the *heat-regulation* of the animal organism. These disturbances of the heat regulation occur most commonly and most pronouncedly in diseases of the thyroid gland. In myxedema the bodily warmth often sinks far below the normal, in Basedow's disease hyperthermia is not rare. In the one the vegetative functions are lowered, in the other increased, the diminished or increased heat production cannot however alone be the cause. There must occur in addition other sorts of disturbances especially in the mode of action of the vessels of the skin; or in the vegetative nervous system, that I shall not go into here on account of its complexity. On the ground last mentioned, it is well also to ascribe to the chromaffin tissue an important rôle in the regulation of heat, as adrenalin, as may readily be demonstrated experimentally, through contraction of the vessels of the skin and prevention of the perspiration may lead transitorily to a significant hyperthermia, even with shivering. Also the hypophysis seems to enter into the regulation of temperature on account of its influencing the vegetative nervous system; to this statement points the fact that in hypophysial dystrophy the temperature also always is instituted at an abnormally low level. I content myself with these few examples; the intimate relation of the ductless glands to the vegetative nervous system, which I shall speak about later, affords without anything else sufficient grounds for this. The same holds true for the *influencing* of the *water economy;* retention of water in myxedema, with throwing off of water in this condition by the use of thyroidin, polyuria in the "hypertonic diathesis," diabetes insipidus in individuals with disease of the hypophysis, diabetes decipiens or high-grade polyuria in diabetes mellitus, all questions which have as yet been very little investigated and the study of which represents many results.

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[1] Increase in weight due to feeding [Mästung].—*Editor.*

## Embryology of the Ductless Glandular System

Before I attempt to group the blood-glands according to their functions, I should like to say a few words as to the *embryology of the ductless glandular system.* It is a shame that this subject has to the present been somewhat neglected by the embryologists. All three germinal layers contribute to the structure of the ductless glandular system. According to the contributions that I have found in the literature, it seems to me that the following grouping is possible:

The chromaffin tissue is of neuroectodermal origin.

The posterior lobe of the hypophysis is also of neuroectodermal origin. The pars intermedia is also of ectodermal origin. It is questionable, however, whether the pars intermedia develops from the anterior or the posterior lobe. In the latter case it would be of neuroectodermal origin.

The anterior lobe of the hypophysis develops from an extrusion of the dorsal wall of the ectodermal primary mouth cavity where it passes over into the entodermal head-gut.

The middle lobe of the thyroid gland develops from the ventral wall of the entodermal head-gut, the lateral lobes apparently in part from the ventral wall of the fourth pharyngeal pouch. The anterior lobe of the hypophysis and the thyroid gland are phylogenetically older structures and were formerly glands with external secretion that poured their secretions into the intestines.

The parathyroid glands are of entodermal origin and develop from the dorsal wall of the third and fourth pharyngeal pouches.

The thymus gland is also of entodermal origin and develops from the ventral wall of the third pharyngeal pouch.

The pancreatic insular apparatus develops from an extrusion from the pancreatic excretory ducts and according to *Weichselbaum* is of entodermal origin.

The suprarenal cortex comes from the epithelium of the body cavity and is of mesodermic origin.

The sexual glands develop from a neighboring site of the celomic epithelium and are therefore also of mesodermal origin; this is generally assumed as true of the interstitial cells, while the glands of generation, according to the views of many authors, develop directly from the primordial cells. The cells of the suprarenal cortex and the cells of the interstitial glands show a certain morphological similarity.

The epiphysis develops from an extrusion of the roof of the third ventricle; it is therefore in part of neuroectodermal origin; in a clinical respect it shows a certain relationship with the interstitial glands and the suprarenal cortex, so that we can believe that it is in part of mesodermic origin.

Hence we may group the ductless glands, according to their origin from the germinal layers, into those of neuroectodermal origin (chromaffin tissue, posterior lobe of the hypophysis), those of ectodermal origin (anterior lobe of the hypophysis), endodermal origin (*a*) from the head-gut (thyroid), (*b*) from the branchial derivatives (parathyroid glands, thymus gland), and finally those of mesodermal origin (suprarenal cortex, interstitial glands, pancreatic insular apparatus). The glands of generation seem, on account of their development from the original primordial cells, to take a special place. Although this grouping is incomplete, still it seems to me that important factors may be derived from it. It is striking that the posterior lobe of the hypophysis (and pars intermedia?) and chromaffin tissue, the active principles of which, adrenalin and pituitrinum infundibulare, show a certain similarity in their action, are both of neuroectodermic origin, and that the anterior lobe of the hypophysis and the thyroid gland, whose relationship in a physiological and pathological sense has been many times referred to, show phylogenetically a certain relationship, in that formerly they were both glands with an external secretion. Finally it is striking that the interstitial glands and the suprarenal cortex that are both of such importance for the development of the secondary sexual characters and stand in immediate relation to premature development both develop from the celomic epithelium. From this standpoint it would be interesting to see whether in eunuchs the suprarenal cortex is not hypoplastic. I am well aware that this grouping of the ductless glands is associated with much that is speculative, but nevertheless it seems to me that their study in this direction is of practical value.

## Grouping of the Ductless Glands

Let us now attempt a classification of the ductless glands according to their *physiological actions.* I first attempted such a classification four years ago, in which I differentiated acceleratory and retarding hormones. This differentiation was founded on observations as to the in many respects antagonistic influencing of the metabolic processes through the hormones or ductless glandular extracts. *Biedl* later used the terms dissimilatory and assimilatory for them. We can also say catabolic and anabolic. This division cannot be carried out for the totality of the ductless glands, yet it seems to me one well adapted for its purpose. I quote the following examples:

The hormone of the thyroid gland we may regard with full right as acceleratory or dissimilatory or catabolic. As far as we know its actions, it quickens metabolism and increases excitability. That in absence of the thyroid in early youth growth and assimilation remain behind does not seem to me to speak against this assumption, as the arrest in growth is to be regarded only as the effect of serious inhibition of all metabolic processes.

Also the hormone of the chromaffin tissue is of pronounced acceleratory or catabolic action. It increases the excitability of the sympathetic nerves—decomposes glycogen, increases the respiratory metabolism, etc. (the more intense formation of glycogen in the course of a chronic adrenalinizing I regard as only a secondary one, through compensatorily increased activity of the pancreatic insular apparatus).

Also the posterior lobe of the hypophysis belongs to this group of ductless glands, at least we must regard the actions of the pituitrinum infundibulare as pronouncedly catabolic or dissimilatory.

To this group we may oppose the glands with retardative or anabolic or assimilatory hormones. To the latter belong the pancreatic insular apparatus, that controls the building up of glycogen and also the assimilation of fat, and diminishes the excitability of the sympathetic nerves (*Löwi*); further the parathyroid glands, that probably assist the assimilation of calcium in the ganglion-cells and at the same time reduce their excitability. Both work assimilatory and excitability diminishing, each however in a specific way; in the diseases due to absence of both glands sometimes cataract formation occurs.

Probably to this group belongs also the anterior lobe of the hypophysis, the extract from which reduces the fundamental exchange and the functional increase of which brings about, as is known, an abnormal growth energy in the bones and soft parts. Further I might here include the interstitial glands, as they influence the ossification of the epiphysial junctures, the growth of the larynx,[1] etc.

I might express the opinion that the generative glands on the contrary belong to the catabolic group, as in the inhibitions of growth that occur after removal of the interstitial glands as, for example, by X-ray, only the generative glands are damaged; further we shall see in the chapter on the sexual glands that in the premenstrual period in women, all life processes are increased with the ripening of the follicle; further it is probable that in man, too, tonic excitability-increasing influences proceed from the generative apparatus.

Thymus gland and epiphysis probably belong to the anabolic group.

If this division, which I regard as speculative, is confirmed by further investigation, they would lead to a result that appears to me to be very significant. As is known, the ductless glands are for the most part arranged in the organs in pairs. It would then be seen that the pairs regularly belong to different groups. This is well shown in the accompanying diagram.

| Acceleratory group (catabolic-dissimilatory) | | Retardative group (anabolic assimilatory) | |
|---|---|---|---|
| Germinal layer | Ductless gland | Ductless gland | Germinal layer |
| Fore-gut | Thyroid gland | Parathyroid | Pharyngeal pouch |
| Neuroectodermal | Posterior lobe of hypophysis | Anterior lobe of hypophysis | Ectodermal |
| Neuroectodermal | Chromaffin tissue | Suprarenal cortex | Mesodermal |
| Primordial cell | Glands of generation | Interstitial glands | Mesodermal |

## Relation between the Ductless Glandular System and the Nervous System

I finally consider the *relations between the ductless glandular system and the central nervous system.* The most recent years have furnished an abundance of observations and ideas just in this direction, but these observations and ideas are still very unclear and contradictory, so that a concise consideration of this subject is hardly possible without strong subjective coloring.

I shall not consider more intimately here the manifold reciprocal influences that are already furnished by the spatial relationship between many of the ductless glands and the nervous system (for example pressure action on the mid-brain by hypophysial and epiphysial tumors, and of brain tumors on the hypophysis and epiphysis).

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[1] *Novak* has quoted just the sexual glands as an example to show that we are not yet prepared for a division into an acceleratory and retardative group. He says: If after the removal of a sexual gland we cause an increase in growth and at the same time find a decrease in beard formation and inhibition in the growth of the larynx, is then the gland growth-inhibiting or growth-increasing?

If, however, we regard the increased growth only as a result of the delayed epiphysial closure, we find that all effects of the removal of the interstitial glands in youth are growth-inhibiting.

### A. Influence of the Ductless Glandular System on the Nervous System

Very significant is the influence of the ductless glandular system on the psychical and mental functions. This subject has been dealt with very often in recent years, for instance, by *Laignel-Lavastine*, *Bauer*, *Marburg*, *Münzer*, and *others,* and recently a considerable study has been published on the subject by *v. Frankl-Hochwart.*

I refer to the alteration in character this is almost always associated with the development of Basedow's disease, to the psychical irritability, the inclination to irascibility, the manic-euphoristic attitude of these individuals; to the apathy and the lack of interest of the myxedematous; to the characteristic quiet mental attitude in hypophysial dystrophy, and the feeling of mental want of strength in those suffering with Addison's disease; to the depressive attitude of the tetanic, and finally to the profound influence that the ripening of the sexual glands at the time of puberty or the loss of function of the sexual glands in castrates exercises on the psyche.

The relations of the ductless glandular system to the *vegetative nervous system*, as we shall see later, are not only important for the pathogenesis of many a ductless glandular disease, but the knowledge of the same possesses also a great practical interest through the fact that in many ductless glandular diseases the solution of the individual symptom-complexes is in many respects simplified. These relations are of two kinds:

1. The ductless glands themselves are vegetative organs. They are supplied by vegetative nerves and possess, therefore, central projection fields. It is to be assumed that the function of the ductless glands is in great measure regulated by the nervous system.
2. The ductless glandular system influences the excitability of the vegetative nervous system by the hormones that it gives off to the circulation. At least this has been ascertained with certainty with regard to adrenalin, and is in probability true of the other ductless glandular hormones. I shall take up this point first. But before this I wish to say something as to the anatomy and physiology of the vegetative nervous system.

As is known, the vegetative nervous system supplies chiefly the organs with smooth muscle fibers. In its function it is partially independent, in great degree, of the central nervous system. While the somatic or animal nerves pass uninterruptedly from the central nervous system to their organs of supply, the vegetative nerves are always interrupted in the vegetative ganglia. We hence distinguish preganglionic and postganglionic vegetative neurons. *Langley* divides the vegetative nervous system into two groups, according to anatomical relations, into the cranio-sacral and the sympathetic groups. He terms the whole vegetative nervous system autonomous and the group of the cranio-sacral autonomous nerves parasympathetic, the other group sympathetic. The Viennese authors, who have busied themselves much with this question, call the cranio-sacral autonomous nerves without further ado autonomous, hence distinguishing between autonomous and sympathetic nerves. This terminology has secured a large foothold in the German literature. The disturbance in these two groups depends upon an extensive difference not only in their anatomical relations, but also in their physiological behavior. The action of both groups on the organs they affect is in great part an antagonistic action. While for example the sympathetic accelerator nerve accelerates heart action, heart action is slowed by the autonomous vagus nerve. While the sympathetic splanchnic nerves inhibit the peristalsis of the intestine, this is reinforced through irritation of the autonomous vagus. The following scheme, which is taken from the experimental pharmacology of *H. H. Meyer* and *R. Gottlieb*, shows these relations in a manner that may be readily understood (p. 26).

The two groups also are different in a most noteworthy manner in their behavior toward certain pharmacological agents. Indeed there has been based on this difference a pharmacologic test of function that should furnish evidence as to the condition of excitability of the vegetative nerves. As it is also used in affections of the ductless glands I shall here briefly detail the most important facts.

Nicotine shows a specific affinity for all vegetative nerves, but only for the preganglionic fibers, in that it interrupts conduction in these fibers.

Adrenalin acts as a stimulant to the myoneural junction of the sympathetic nerves in all their organs of supply and indeed is furthering or inhibitory, according as the activity of the organ of supply is furthered [fördern] or inhibited by electrical stimulations. Only the sweat-glands are not, when the doses are not too large, influenced by adrenalin. On the contrary, ergotin shows a specific affinity for the furthering sympathetic fibers, while the inhibitory fibers remain unaffected.

On the contrary, pilocarpine, muscarine, physostigmine, and cholin act as stimulants on all the autonomous nerves, but only the sweat-glands innervated by the sympathetic are energetically stimulated by these agents. Picrotoxin acts similarly, but with a central point of attack. On the contrary, atropine acts as a paralyzant on the autonomous nerves and also inhibits the activity of the sympathetically innervated sweat-glands.

The fact that among the substances mentioned there is a true hormone, adrenalin, leads us to expect that this direction of investigation is very important for the internal secretions. In addition specific affinities for the vegetative nervous system are shown by certain ductless glandular extracts not well defined chemically.

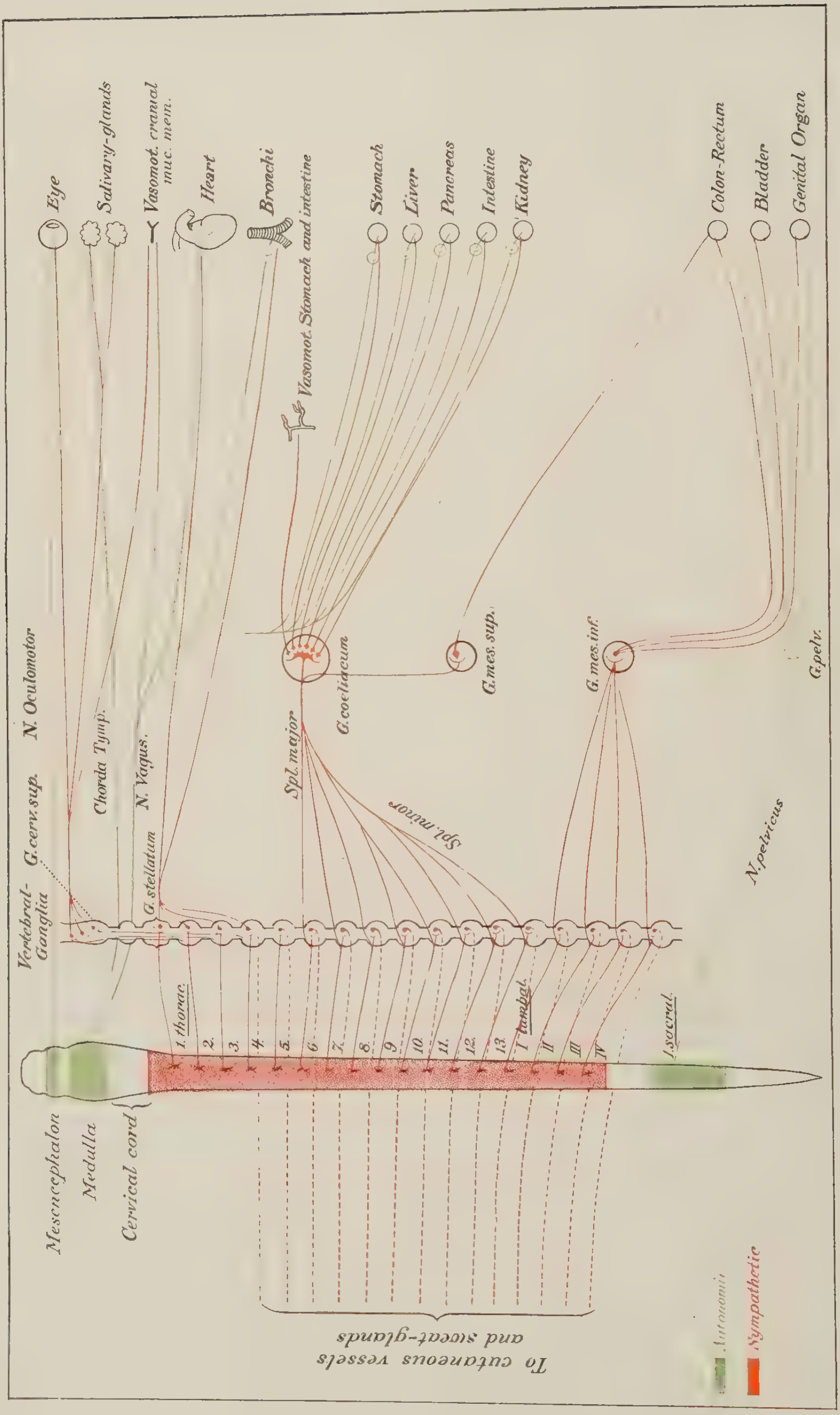


FIG. 2.—Diagram of the vegetative nervous system (according to *H. H. Meyer* and *R. Gottlieb*). The autonomous innervation is colored green, the sympathetic red.

Let us examine more closely the action of these hormones or ductless glandular extracts in this direction.

Of adrenalin, the internal secretion of the chromaffin tissue, it has already been mentioned that it is of great significance for the excitability of the myoneural junctions. As in a genetic relationship the chromaffin tissue belongs to the sympathetic system, this system possesses within itself a regulator of its excitability. (*Bayliss* and *Starling*.) As for the physiological significance of the chromaffin tissue, it must furthermore be considered that by the lasting function of this tissue there is maintained a certain distribution of blood. The sympathetic innervation of the different vascular districts is of different richness; for example, the vessels of the muscles and skin arê very abundantly supplied, while the vessels of the lungs, of the coronary arteries, and of the brain possess a weak sympathetic supply. *Priestley* and *I* have pointed out that the venous blood emanating from the organs with a rich sympathetic innervation are adrenalin-free or are essentially poorer in adrenalin than the arterial blood flowing to them. The liver is supplied with blood rich in adrenalin only by the hepatic arteries, while the very much larger amount of blood that flows to it through the portal vein is adrenalin-free or at least poor in adrenalin, as this blood has already passed through the capillary system of the intestine. Hence in a quiet fasting organism there occurs a definite blood distribution, a distribution that may be regarded as very much to the purpose. Thus the resting organs (muscle, skin, intestine, etc.) contain very little blood, while those organs whose activity is necessary for the maintenance of life (heart, central nervous system, lungs, liver, etc.) are relatively rich in blood. The former become supplied with more abundant blood, through the regulatory activity of the sympathetic simultaneously with increased cardiac activity, only when they are functionally more in demand.

The chromaffin system plays an important rôle in the regulation of the blood's plasma contents. After the injection of large amounts of adrenalin, *Bertelli*, *Schweeger* and *I* saw an appreciable increase in the count of the red cells of the circulating blood. As this hyperglobulia survives the vaso-contraction for a long time, the cause of this is to be sought not only in the pressing-out of the plasma, but also in an alteration of the permeability of the vessel wall on account of which the return-flow of plasma is delayed for a long time. Now it is known that in individuals who are brought relatively rapidly into an atmosphere poor in oxygen (mountains, ballon-trips, etc.) the number of red blood cells increases very rapidly. The hyperglobulia brings about greater respiratory surface, this counterbalancing the slighter partial pressure of the oxygen. To-day it is generally assumed that at least in rapid transitions it is not the result of the increased production of erythrocytes. We believe rather that it is due chiefly to a regulatory exudation of plasma into the tissues and that in this regulation is involved the chromaffin tissue.

Finally, our investigations have shown that injection of adrenalin produces neutrophilic hyperleucocytosis and induces a disappearance of the eosinophiles from the circulating blood. Whether this is due directly to excitation of the sympathetic nerves or indirectly to alteration in the distribution of blood is hard to decide. I would only point out that the curves of the white and red cells are not parallel throughout, and that we can show that drugs such as pilocarpine and cholin always in the first stage of their action lead to an appreciable relative and absolute increase of the mononuclear cells, eventually also to a changed distribution of the neutrophilic cells in the vascular tree, in that these accumulate in the organs less well innervated by the sympathetic, such as lungs and the liver, while there is less of them in the vessels of the skin and muscles. Hence the chromaffin tissue seems to exercise a regulatory influence on the activity of the blood-forming apparatus, chiefly through excitation of the medullary system [of the bones].

The actions of thyroidin on the nervous system are far more manifold than those of adrenalin. We must, however, refer most of the various symptoms of hyperthyroidism to alterations of tonus in the organs supplied by the vegetative nerves, for example, the tachycardia to excitations of the sympathetic accelerator nerve, the marked fall in blood-pressure to diminution of the vascular tonus in the muscles, skin, and intestinal vessels, the irregularity of the breathing to a heightening of the vagal tonus, the sweats to an excitation of the nerves of the sweat-glands, etc., etc. Probably the excitability throughout the entire vegetative nervous system is increased, although an elective affinity for definite sympathetic or autonomous nerves is unmistakable.

The same holds true for extracts of the hypophysis. The pituitrinum infundibulare, obtained from the posterior lobe, works as an increaser of blood pressure and as a strong diuretic; it also acts as a slower of the pulse through excitation of the vagus, and as an increaser of excitability of the autonomous nervus pelvicus, moreover as an increaser of the excitability of the uterus, etc.; here also exist elective affinities for certain vegetative organs supplied by the sympathetic or autonomous nerves.

Pituitrinum glandulare, according to our investigations, changes the distribution of the blood in the opposed sense. It reduces blood-pressure and lessens the volume of the liver.

Let us now consider the alterations of the excitability on the tonus of the vegetative organs in the ductless glandular diseases.

In Basedow's disease there is an abundance of symptoms that depend on an increased tonus of both the autonomous and the sympathetic vegetative organs, for example, the tachycardia, the eye symptoms, the sweats, the increased falls of blood-pressure, etc., etc. As these symptoms are found in more or less pronounced manner in artificial thyroidism, the conclusion is justified that they are produced also in Basedow's disease by an increased production of the secretion of the thyroid gland. Reversely, in typical myxedema the vegetative functions are found to be delayed, slow; the excitability of the organs supplied by the sympathetic and autonomous nerves is reduced (slower pulse, sluggishness of the intestine, etc., or reduction of the glycosuric action of adrenalin, absent or deficient hyperglobulia after the injection of adrenalin, reduced action of pilocarpine, etc.).

Also the parathyroid bodies influence the excitement or excitability of the vegetative nerves. In the acute stage of tetany are found hyperglobulia, spasmodic conditions of the stomach and intestines, the bladder, ciliary muscles, the heart, etc. The different actions of sympathicotropic or automonotropic agents, such as adrenalin and pilocarpine, are essentially strengthened. The circumstance that in tetany the manifestations on the part of the vegetative organs are essentially different from those of Basedow's disease shows that the affinities for the vegetative organs displayed by the hormone of the parathyroids and the hormone of the thyroid are electively different; and also the point of attack in the neuron is different, as in the one case the hyperirritability [or hyperexcitability, Überregbarkeit], the other the hyperexcitement [Überregung] is more prominent.

In Addison's disease, as is to be expected there is shown a reduction of the excitability and a slighter tonus of the organs innervated by the sympathetic, and especially prominent are the reduction of the blood-pressure and the lessened action of adrenalin. Here the picture is complicated by a number of symptoms depending on a strong excitement of the vegetative organs, symptoms the genesis of which is as yet doubtful.

In the rest of the ductless glandular affections these relations are still less apparent. I shall report the pertinent investigations and observations in the appropriate chapters, and here shall only indicate the following: In hypophysial dystrophy and in eunuchoidism the excitability of some of the vegetative nerves seems to be somewhat decreased. Probably there exists a certain sluggishness of the vegetative functions, which however does not attain the degree of sluggishness of those in myxedema. Diabetes insipidus, which not rarely is associated continuously or temporarily with diseases of the hypophysis seems to depend on an irritation of the posterior lobe of the hypophysis or on a specific increase of the function of the kidneys. In acromegaly are found not rarely profuse sweats, also when there are otherwise no manifestations of complicating hyperthyroidism. In some cases of diabetes mellitus, *Löwi* has shown an increased excitability of the dilator pupillæ, which is innervated by the sympathetic; we found in a definite category of cases which perhaps are similar to *Löwi's* cases a strikingly strong glycosuric action of adrenalin; in such cases, in which the also neurogenous factor of the glycosuria markedly predominates, there are sometimes found also an increase of blood-pressure (hypertonic diabetes).

Also the glands of generation seem to exercise an important influence on the tonus of the vegetative organs. This comes especially to expression in the female sex, in the form of the known wave-movement. With maturation of the follicles (especially of the fertilized ovum in pregnancy) there occurs an increased vitality of the whole organism, an increase of the vegetative functions that comes about in part indirectly through the higher activity of the whole ductless glandular system. At the climacteric, when the generative glands discontinue their function, there occurs in woman known lability of the vegetative nervous system, especially of the vasomotors, a sort of vasomotor ataxia that first disappears again with the complete loss of ovulation. Also in men there sometime occurs, very rarely, however, climacteric disorders.

Especially distinctly set in at the time of puberty, the increase of vegetative functions, with the enormous development of the glands of generation, again rather more strong in woman than in man, often in an incoordinated manner, gives occasion to various disturbances. In specially predisposed female individuals the revolutions in the organism at this time lead to an exhaustion which seems to stand in relation with the development of chlorosis.

In the other ductless glandular diseases the behavior of the vegetative nervous system is still less clarified. In premature development on account of pineal, suprarenal cortical, or sexual glandular tumors this pubertal increase of the vegetative functions is probably anticipated. We cannot state anything certain as to the influence of the thymus gland on the vegetative nervous system.

This condensed survey suffices well to show to what extent the activity of the vegetative organs and the excitability of the vegetative nervous system is influenced by the ductless glands. This direction of investigation has just been determined on. As to its further development, especially when physiological chemistry has established for us still more hormones, there is to be expected a deepening of our knowledge as to the symptomatology of the ductless glandular diseases. From the observations up to the present, however, it may be stated, although with insufficient surety, that the affinity of the hormones for the vegetative nerves is an elective affinity; not adrenalin itself influences the entire sympathetic group, for it leaves the sweat-glands unaffected. The other ductless glandular extracts, as we know, always show especial elective affinities for certain organs, whether these are supplied by sympathetic or autonomous nerves; clinical observations furnish still more evidence to this effect. Hence it seems to me improper to draw too extensive conclusions from the pharmacological tests of function. Certainly they have furnished us with very valuable inferences, and have provided a deep view into the functions of the organ innervated by the vegetative nervous system. For example: *Löwi's* reaction is as good as constant on the dog without a pancreas, as is also the reduction of the excitability of the sympathetic nerves after extirpation of the thyroid. This is evidenced not only by the diminished glycosuric action of adrenalin, but also by the remaining absent of a marked hyperglobulia. This also holds good for typical myxedema so far as it remains uncomplicated by pathological correlations, for example by a tetany. However, I believe on the contrary that we would not be just to the complex relationships if we were to draw from the result of such functional tests a conclusion as to the condition of excitability of the whole sympathetic or the whole autonomous group. In this respect I would not subscribe to the views of *Eppinger* and *Hess* so far as these views are concerned with diseases of the ductless glands. These are based chiefly on the observations that in individuals in whom adrenalin works diuretically, the action of pilocarpine remains absent, and reversely that in individuals who show a strong pilocarpine reaction, adrenalin does not produce glycosuria. The absence of a glycosuric action of adrenalin does not show that the entire sympathetic group is hyposensitive. Adrenalin acts as a raiser of blood-pressure, accelerates cardiac action, acts as a diuretic, produces aneosinophilic hyperleucocytosis, etc., etc. The glycosuric action is only a partial manifestation of a very manifold action-complex. Besides this, hyperglycemia and considerable increase of the respiratory quotient can occur without glycosuria, if diuresis does not come in the way; and besides, glycosuria may remain absent in cases where the consumption of sugar is high. We saw, for instance in the acute stage of tetany, absence of glycosuria in spite of enormous vascular action. In other cases we may observe marked glycosuria, while the vascular and cardiac action remain almost entirely absent. In bronchial asthma I never saw glycosuria after the injection of adrenalin, but on the contrary the hypereosinophilia which was often present was diminished markedly. Also the other active ductless glandular extracts, as for example, thyroidin, show such a dissociation of their action.

The relations are rendered still more complex by the fact that individual organs are innervated by furthering [fördern] as well as inhibitory fibers of the same group. As *Elliot* has shown, adrenalin in minimal doses produces vascular dilatation, and only in large doses vascular contraction. Pituitrinum infundibulare increases the peristaltic wave-movement of the gravid rabbit uterus. The same extract acts for the most part inhibitory on the virginal rabbit uterus. I can therefore agree with *Eppinger* and *Hess* when they assume in an insufficiency of the chromaffin tissue a relative preponderance of the autonomous innervation. But even in Addison's disease (perhaps through failure of the cortex, perhaps through other as yet obscure factors) there may occur acute, highly complex conditions of excitement in the vegetative nervous system.

In many later works there is found the tendency to distinguish between vagotonic and sympatheticotonic conditions in ductless glandular diseases. For instance, *Adler* supposes after the failure of the sexual glands a sympatheticotonic condition, on account of the fact that he found glycosuria in certain castrated individuals after the injection of relatively small doses of adrenalin, while pilocarpine for the most part did not cause sweating; and he regards the complicated process in the vegetative nervous system in dysmenorrhea as vagotonic. I do not believe that these things allow of such a grouping.

## B. Influence of the Nervous System on the Function of the Ductless Glandular System

I now come to the consideration of those relations between the ductless glandular system and the nervous system that are characterized by the fact that the ductless glandular system is itself vegetative, that it is made up of organs supplied by vegetative nerves, that possess central projection-fields. We shall have investigated in what measure activity of the ductless glandular system is regulated by the nervous system. Our knowledge as to this kind of relationship is as yet very deficient. We may scarcely put aside the supposition that in this respect the ductless glands behave very differently. The impulses emanating from the central nervous system are very important for the activity of the chromaffin tissue, for example, perhaps a regulated activity is not possible even for a short time if the central innervation is wanting. Centers for these ductless glands lie on the floor of the fourth ventricle and according to the latter investigations of *Aschner* also in the subthalamic region. Stimulation of these centers leads, just as the stimulation of the nervous paths proceeding from them to the chromaffin tissue, to the dissemination of adrenalin. *Priestley* and *I* have shown that after interruption of these paths by transection of the lowest cervical cord the amount of sugar in the blood rapidly decreases; it seems therefore that the activity of the chromaffin tissue is discontinued, if its connection with central projection-fields is interrupted. The number of experiments is not at all great, as the operative attack is difficult. It seems to me, however, noteworthy that indications are wanting that after this attack which also deprives the insular apparatus of its central innervation, during the short time that the animals survive the attack, disturbances in the insular apparatus occur. I would not at all make the statement that the activity of the insular apparatus is not regulated by the central nervous system, only it seems as though this influence were very much slighter; the insular apparatus seems very much more, also after interruption of its connecting paths, for some time to be able to continue its activity. It seems to me very much to the purpose that the production of the assimilatory hormone is accessible to few nerve influences; such ductless glands always seem to work with a certain surplus, while the giving off of the dissimilatory hormone must be very finely graduated in order to do justice to the rapidly changing demands; this is only possible, however, if the central nervous system governs the function of the ductless gland concerned.

That the activity of the thyroid gland is dependent on the central nervous system may be concluded from the older literature. How otherwise can we explain that existence of an acute Basedow's disease with the rapidly developing thyroid swelling, that comes over night? Newer investigations of *Asher* and *Flack* make it very probable that the nerves regulating the thyroid glandular activity run in the nervi recurrentes. These investigations also make it seem possible that rapid variations in the function of the thyroid gland come about through nervous influence.

Nothing as yet is known in this connection with respect to other ductless glands. I must discuss a little more thoroughly only the sexual glands. The sexual glands seem to assume an individual position by virtue of their independence of the central nervous system. At least the results of transplantation experiments up to the present would seem to indicate this. With the thyroid gland only autotransplantation is successful, that is the transplantation of the thyroid gland to another place in the same individual. Homiotransplantation (transplantation to another individual of the same kind) fails. But up to the present it has not been possible to maintain autotransplants capable of retaining their function, even when their vessels are united directly with the vessels of the part by means of suture. This shows, provided of course, that the efforts of the surgeons are not crowned with success at some time in the future, that the function of the thyroid gland is not possible for a length of time without connection with a central projection-field. It is different with the sexual glands. Here in many cases not only autotransplantation, but also homiotransplantation succeeds. Indeed here even the results of heterotransplantation far surpass all that has been seen on the transplantation of the other ductless glands. This separate position of the sexual glands was really to have been expected. According to the noteworthy views of many authors the generative glands originate from the primordial cells, which through division of same preceding cells, the ovum and the spermatozoon, are organisms in themselves and lead an independent life. That the sexual glands are also accessible to influences on the part of the central nervous system and have central projection-field no way contradicts this idea. According to *Aschner* such a projection-field lies in the subthalmic region. On its long-continued excitation degeneration of the sexual glands occurs. Indeed it may be supposed that the hypophysis furnishes trophic influences to the sexual glands by way of the blood.

If we summarize the little we know concerning this important subject we find that the *ductless glandular system shows a certain degree of autonomy, which, however, is developed in very different ways on the part of the individual ductless glands. The sexual glands are provided with the greatest degree of autonomy, the chromaffin tissue with the least.*

### Influence of the Ductless Glands on the Hematopoietic Apparatus

Before I speak of the significance of the influences just described on the pathogenesis and etiology of the ductless glandular affections, I would like to make a few remarks on the influence that the ductless glandular system exercises on the activity and development of the *hematopoietic apparatus.* I should like to make emphatic the fact that the thyroid secretion is necessary for a normal development and activity of the hematopoietic apparatus. In myxedema and still more in thyroid glandular insufficiency in youthful years do disturbances in the formation of blood occur. Especially in infantile myxedema does there come about a degree of anemia which is often not inconsiderable, and a reduction of the erythrocyte count and the amount of hemoglobin; the involution of the lymphatic apparatus is insufficient; in the blood picture the neutrophilic leucocytes retrogress, and the mononuclear and eosinophilic predominate. On the administration of thyroid extract these disturbances disappear wholly or at least in great part. Also in other diseases due to absence of glandular extracts, disease such as hypophysial dystrophy and eunuchoidism, similar manifestations occur, although they are much less well pronounced. The production of neutrophilic granulocytes hence seem to require a furthering influence on the part of the thyroid gland and chromaffin tissue. From this fact are elicited relations of the ductless glands to the so-called status lymphaticus. The significance of a hypoplasia of the chromaffin system for this condition has been mentioned by especially *Wiedel*, *Hedinger*, and *Eppinger* and *Hess*.

A noteworthy influence on the hematopoietic apparatus is exercised by the increase of function of the thyroid gland. The finding of *Kocher*, that the count of mononuclear cells in the blood considerably predominates, belongs to the most constant symptoms of Basedow's disease. In addition to this relative and mostly also absolute increase in the mononuclear cells (sometimes also the eosinophiles) there is found, just as frequently, however, an absolute diminution of the neutrophilic cells in the circulating blood. Often the relative increase of the former is only the sequel of the absolute diminution of the latter. It seems to me that in this connection should be mentioned the fact that *Bertelli* and *I* after the administration of thyroidin to dogs found an accumulation of neutrophilic cells in the blood of the liver. It seems therefore that thyroidin influences the distribution of blood in the vascular tree. The alterations in the blood picture in Basedow's disease are therefore not analogous throughout to those of myxedema, which is best explained by the fact that on administration of thyroidin in myxedema the blood picture approaches normal, while in Basedow's disease it diverges from normal (*Falta*, *Newburgh*, and *Nobel*). We are dealing in the first case with symptoms of absence, in the latter case with irritative manifestations.

As, as has already been described, sympathicotropic and autonomotropic substances influence the blood picture and the distribution of the leucocytes in the vascular tree in a definite way, we can comprehend the fact that symptoms of irritation in ductless glandular affections and in part also the symptoms of absence are the result of an altered condition of excitability in the vegetative nervous system.

With this agrees the fact that in many nervous diseases that have involved especially or partially the vegetative nervous system, as especially in the vagal neurosis, there have been found mononucleosis and eventually hypereosinophilia, while in hypertonic diathesis, for example, in the initial stage, the count of neutrophilic cells lies at the upper boundary of the normal or even exceeds this.

On long continuance however there are found in many ductless glandular diseases morphological alterations in the hematopoietic apparatus. The alterations in the blood pictures that are observed are at first hand very hard to interpret. It may be stated that in acromegaly there is very frequently found mononucleosis and eventually slight eosinophilia, and we have seen mononucleosis in chronic tetany (in this disease under the influence of acute exacerbation there may occur rapid reversals of the blood picture); and even in severe diabetes may mononucleosis (without status lymphaticus) be observed. I agree with *Borchardt*, who has likewise studied these relations, that in general in most of the ductless glandular diseases there is observed a tendency to mononucleosis and neutropenia, and in many a slighter or severer grade of status lymphaticus.

## Pathogenesis and Etiology of the Ductless Glandular Diseases

On turning our attention to the consideration of the *pathogenesis* and *etiology* of the ductless glandular diseases, we find the idea we have developed as to the influencing of the function of these glands by the nervous system is not without significance. However, the etiology of a great number of ductless glandular diseases is to be sought in an entirely different direction. Let us first consider the diseases due to absence or deficiency. Here we meet with congenital aplasia or marked hypoplasia of the ductless gland, for instance, in thyroaplasia. A defective development [of a "rudiment" or "Anlage"] often seems to be a favorable soil for a later infection. *Wiesel* for instance assumes that a tuberculosis infection very frequently becomes established in the suprarenals on hypoplasias of the chromaffin tissue. But on such a defective mapping-out an insufficiency may become manifest, temporary or permanent, even without the addition of an infectious process, if larger demands are made on the ductless gland in question; for example, glycosuria may occur on marked alimentary overloading with carbohydrates if an (often hereditary) weak mapping out of the insular apparatus is present. Further, trauma should be mentioned. This, for example, may affect the testicles and lead to eunuchoidism or late eunuchoidism; in operation on goiter too much of the functionating thyroid glandular tissue may be extirpated, or the parathyroid glands may be injured; a very great rôle in the pathogenesis of the disease due to absence is placed by infection. Tuberculous, luetic, or other bacteriological processes, most as yet not investigated, may temporarily damage the ductless glands or lead to permanent destruction or sclerosis. These infectious processes may spread to the ductless gland from the neighborhood, they may affect the acini of the pancreas through the ducts and involve the insular apparatus by contiguity; in most cases, however, the infection follows by the hematogenous route; in many cases in which the infectious process involves many ductless glands at a time and causes destruction (multiple ductless glandular sclerosis) a congenital or acquired predisposition of the ductless glandular system is perhaps present. Also chronic intoxications, as alcoholism, poisoning by the toxin of goiter, etc., may damage single or several ductless glands. Furthermore, tumors that proceed from parts in the neighborhood or from the ductless gland itself, may destroy the functionating tissue. In addition in many ductless glands, purely functional disturbance on a nervous basis are possible, analogous to those hyposecretions that we know in glands with external secretion. The possibility of a functional Addison's disease was long ago discussed by *v. Neusser.* A like supposition seems to me also debatable for the chromaffin tissue or for pancreatic insular apparatus. Also trophic degenerations of the ductless glands would not be impossible.

A greater importance seems to me should be ascribed to nervous influences in the pathogenesis of the diseases of hyperfunction. The pathologico-anatomical correlate of hyperfunction is hyperplasia, or in ductless glands of definite morphological structure, of adenoma formation. The latter is found in the disease of hyperfunction of the glandular hypophysis, of the thyroid gland, the suprarenal cortex; in the sexual glands sarcomatoid tumors are more often found. Hyperplasia of the chromaffin tissue is found in the hypertonic diathesis. Even where, however, the adenoma formation is most common, indeed constant, can a nervous cause of the hyperfunction not always be precluded in peracute Basedow's disease, the entire symptom-complex and the swelling of the thyroid gland can develop in a few hours; here we cannot well blame the adenoma formation, as it is very much more likely that in such cases the adenoma formation sets in at some later stage of the disease; from such cases and from the fact that many symptoms of Basedow's disease, for instance the marked exophthalmos, can hardly be produced by hyperthyroidization have led certain authors back to the conception of the older French authors, according to which Basedow's disease was regarded as a vegetative neurosis and in which many of the symptoms of the Basedow's were considered as coordinated with the hyperthyroidism. According to this we might distinguish Basedow's disease as a hyperthyrosis from the symptom-complex of hyperthyroidism. Whether such views are to be applied to the adenomata of the hypophysis and suprarenal cortex can hardly be decided at the present time. As far as severe diabetes is concerned, we can hardly get away from the assumption of a hyperfunction, whether it be secondary or primary. In Chapter XIII the opinion will be advocated that the entire apparatus regulating sugar metabolism (central projection-fields, pancreas, and chromaffin tissue as organs affected by these fields) is diseased, in the course of which disease process diminution of function in one part and excess of function in another come to exist in juxtaposition.

Even if we transfer the cause proper of the hyperfunction of the organ itself to the central projection-field of the organ, the cause itself is naturally not as yet explained. The problem is only shifted although it cannot be denied that in this manner the solution of the symptom-complex is made easier, or indeed first made possible.

## Relation between Diseases of the Central Nervous System and the Ductless Glandular System

The knowledge that the ductless glands as vegetative organs indeed show a certain autonomy, but in part as far as their function is concerned stand under control of the central nervous system; together with the supposition that we have to reckon with the possibility of a purely functional increase or decrease of their secretion, requires of us that we now investigate whether in the diseases of the central nervous system alterations of the ductless glands are demonstrable. The investigations should foremost of all be important for neuroses of the vegetative nervous system, but must also reach to the psychoses and the other diseases of the central nervous system. So far as the psychoses are concerned there have been pointed out very recently appreciable variations in the condition of excitement and the tonus of the vegetative organs. I refer, among other investigations, to the investigations of *Pötzl*, *Eppinger*, and *Hess*, who have found in melancholia a reduction in the excitability of the vegetative nervous system, and in mania, especially during the first attack, appreciable heightening of the excitability of the vegetative nervous system. Also in other diseases of the central nervous system, for example in tabes, symptoms on the part of the vegetative nervous system become conspicuous in the disease picture.

This investigation seems to have so much the more force because later observations always confirm the more the view that in diseases of the nervous system and in the psychoses, the metabolism is often altered in a profound way. I would here quote some examples. *Rosenfeld* first established that a considerable nitrogen retention occurs in catatonics. *Siege* found enormous variation in the nitrogen elimination in the circular psychoses. Especially intensive studies on metabolism have been made by *Kaufmann* from *Anton's* clinic. Especially mentionable are for example the enormous variations in body weight in psychoses: for instance *Kaufmann* found rapid fall of the body weight in spite of copious forced feeding. According to *Kaufmann* such rapid variations are to be referred chiefly to disturbances in the amount of water in the organism in the wake of nervous influences. In hysteria, *Kaufmann* also found considerable variations in the amount of urine and in body weight and the psychical disturbances in these diseases may have receded, while the vegetative disturbances are still present. Also in progressive paralysis, in tabes, and in a series of other brain diseases are alterations of the metabolism observed—*Paghini* found in many brain diseases increase of the elimination of endogenous uric acid and of the xanthin bases. *Löwe* found increase in the elimination of phosphorus after epileptic attacks and in definite phases of the paralysis and in delirium tremens. The thought has also been expressed that in brain diseases the appreciable indicanuria that occurs is sometimes of nervous origin. There are also observed in cerebral and mental diseases considerable variations in the salt metabolism. As is known, there is frequently found in neurasthenia considerable increase in the elimination of calcium. The brittleness of the bones that is so often seen in tabes indicates a considerable loss of calcium and phosphorus. Disturbances in the carbohydrate metabolism (especially appreciable lowering of the assimilation boundary) are in cerebral and mental disturbances frequent phenomena. Disturbances of the regulation of the heart are not at all a rare symptom. In progressive paralysis *Kaufmann* often found hyperthermia, and in the akinetic diseases as well as after epileptic attacks reduction of temperature. These few examples might suffice. It can well be conceived that these alterations in metabolism come about through a functional influencing of the ductless glandular system.

Special attention has been devoted in this respect to the behavior of the ductless glands in the neuroses of the vegetative nervous system. *Egger* saw in the vasomotor psychoneuroses increases of temperature that lasted for months and years. In visceral neuroses, *Pollitzer* saw positive alimentary galactosuria, while alimentary glycosuria was negative. This reminds one of the alimentary levulosuria described by the author in some cases of Basedow's disease, or in the disturbances in the qualitative decomposition of albumin in tetany. *Curschmann* saw a case of bronchial asthma with intermittent exophthalmus, tremor, and tachycardia. In the vagal neurosis I regularly found appreciable mononucleosis of the blood, and *Eppinger* and *Hess* observed also hypereosinophilia. In the vasomotor neurosis *Roth* found in addition to marked lymphocytosis and lability of the pulse, also lability of the temperature. The fact is quite unexplained why rare cases of pentosuria and isolated levulosuria are almost always associated with vasomotor neurosis. A short time ago I saw a case of pentosuria with pronounced *Herz's* vasomotor ataxia.

In *Raynaud's* disease is often seen slight rise in temperature, distinct trophic and secretory disturbances, and in the attack often marked rise in blood-pressure; sometimes there is polyuria and in rare cases glycosuria.

Partially related to the vasomotor neurosis is perhaps that group of diabetics in which the neurogenous factor especially predominates in the glycosuria. In this is usually found marked vasomotor excitability, and under circumstances increase of the blood-pressure without nephritis (hypertonic diabetes, see Chapter XIII).

Among the many symptoms of the vasomotor neuroses are found, according to this, those which point to an alteration in the metabolism and in general to a functional influencing of the ductless glandular system. It seems to me that there is wanting in this case any secure foundation for bringing a primary alteration of the ductless glandular system into an etiological relationship.

Of the vasomotor neurosis, *scleroderma* seems to merit a more exact consideration. In this affection there are a series of findings that point to a marked involvement of the ductless glandular system. *v. Strümpell* has pointed out a certain opposition in the symptom picture of scleroderma and acromegaly. In the latter the bones and skin are hyperplasic, while in the former there are processes of shrinkage in both organs. The opinion that the basis of scleroderma is a functional disturbance of the hypophysis, finds according to *Roux*, corroboration through the fact that in this case apparent sclerotic processes are found in the hypophysis. Until the present, however, this case has remained isolated; the opinion is often expressed that scleroderma depends on an alteration of function of the thyroid gland. After *v. Leube* first pointed out the coexistence of scleroderma with Basedow's disease, numerous pertinent cases have been found in the literature, which have been compiled by *Sattler*. *Cassirer* mentions, however, that in these cases the diagnosis Basedow's disease is to be accepted with caution, as important symptoms of Basedow's disease, such as pigment displacements, changes in the thyroid gland, irritability of the heart also belong to scleroderma in itself. Even the exophthalmus may be simulated by the sclerodermic mask. *Cassirer* himself calls attention to the fact that these symptoms similar to Basedow's do not always follow in their intensity the course of sclerodermic process. The occasional appearance of myxedemic symptoms (*Grasset*, *Osler*, *Déhu*, *et al.*) and the not rare finding of sclerotic changes in the thyroid glands of those sick with scleroderma have permitted *Jeanselme*, *Singer*, *Hectoen*, *v. Notthafft*, *Leredde* and *Thomas*, and *others* to regard the cause of the scleroderma as an insufficiency of the thyroid gland; the more likely as in many cases good results are obtained by thyroid medication. The common occurrence of pigmentations in scleroderma seems to indicate the associated involvement of the chromaffin tissue. The pigmentations may simulate those of Addison's disease. In not rare cases there are also observed typical smoke-gray discolorations of the mucous membrane of the mouth. In a large number of cases the combination of scleroderma with Addison's disease has also been assumed, although there are numerous observations (*Lichtwitz*, *Kren*, and *others*) of scleroderma with typical Addisonoid pigmentations of the skin and mucous membranes that showed no alterations in the suprarenal glands at autopsy. Finally the combination of scleroderma with tetany has been described in a case of *Dupré* and *Guillain's*. In this case it seems as though a pronounced Addison's disease were also present. As the supposition of change in *one* ductless gland is not satisfactory, there has been upheld by several recent authors a pluriglandular pathogenesis of scleroderma (*Dupré* and *Kahn*, *Rasch*, and *others*). With regard to this, it is conceivable that sclerotic processes in certain ductless glands in scleroderma do not mean very much. The scleroderma often spreads to the deeper-lying tissue and may also extend to the bones and muscles; it is therefore not wonderful if now and then it may involve individual ductless glands; moreover there are found in the majority of cases of scleroderma a great number of manifold symptoms on the part of the vegetative nervous system, condition of excitement of manifold nature, such as vasomotor disturbances, tachycardia, shivering, faintings, rush of blood to the head, feeling of anxiety; as *Klinger* observed, such conditions may occur in attacks. *Hess* and *Königstein* saw in one case of diffuse scleroderma during such attacks an especial sensitiveness against adrenalin and marked excitement of the heart-action, associated with manifestations of acroparesthesia and with subsequent outbreaks of sweat. In addition to this are found in the majority of cases a series of trophic disturbances, as transitory edema, erythema, urticaria, etc. On account of this the diagnosis of a coexistent Basedow's disease is certainly made very much more difficult. On the other hand I do not doubt, however, that in many of the cases there was actually an increase of function of the thyroid gland present, and that it was not at all impossible that the pigmentations had their basis in a disturbance of function of the chromaffin tissue. Nor do I doubt that in certain cases slight symptoms of thyroid insufficiency may occur. When I acknowledge therefore the possibility of pluriglandular symptoms in scleroderma, I would regard them as only secondary, in part due to the sclerodermic process extending over to the ductless glands, and still more due to functional influencing of the ductless glandular system. There are, in addition to this, cases of scleroderma in which the manifestations on the part of the vegetative nervous system are much less prominent.

I agree fully with *Cassirer* in the supposition that in scleroderma the disease process is not primary in the ductless glandular system.

There has also been an attempt to bring another group of diseases, the trophoneuroses, into relation with the ductless glandular system, diseases such as acute circumscribed edema and symmetrical lipomata. In both are regularly found neurosis symptoms on the part of the vegetative nervous system. Here also is found the possibility of functional disturbances on the part of the individual glands, although the symptoms are here less distinctly prominent. This same thing seems to me to hold good for adipositas dolorosa. This condition will be considered in detail in Chapter XIV; here I wish to dispense with the supposition of ductless glandular etiology. The same is true for xanthelasma, the pathology of which *Chvostek* has made the subject of a penetrating study. *Chvostek* in consideration of the occurrence [of xanthelasma] in gradations [schubweise], the kind of distribution, and especially the often rigid symmetry, comes to the conclusion that nervous influences are the basis. The individual with xanthelasma shows a series of symptoms on the part of the nervous system and especially on the part of the vegetative nerves. Here also the changes in the ductless glands seem to me to be only of a secondary nature.

Not only in trophoneuroses, but also in other diseases of the central nervous system, do we find the most manifold symptoms that point to disturbances in the function of the vegetative nervous system. It seems to me that the study of these conditions has been handled rather half-heartedly by neurologists. Myasthenia, paralysis agitans, and myotonia have been brought into etiological connection with the parathyroid glands. As we shall see, however, in Chapter IV, I regard the hypothesis of a primary affection of the parathyroid glands in these diseases as insufficiently supported. Myasthenia, because like scleroderma it is sometimes associated with slight symptoms of Basedow's disease, or tetany (*Tobias*), has been regarded as a polyglandular disease (*Markeloff*), certainly not with more correctness than has been scleroderma. Finally, I wish to make some remarks in this connection with regard to multiple sclerosis, tabes, and progressive paralysis. In multiple sclerosis often symptoms on the part of the vegetative nervous system become distinctly prominent. There often exist tachycardia and great lability of the pulse, mostly pronounced dermographia, furthermore sweats, inclination to hyperthermia, manifestations on the part of the gastro-intestinal canal, polyuria, bladder disturbances, etc. In a series of cases that we investigated we found a great sensitiveness against adrenalin and pilocarpine, often appreciable alimentary glycosuria, strong diuretic action of pituitrinum infundibulare, low degree of tolerance against thyroidin, etc. In some cases even *Chvostek's* phenomenon was observed. It is further known that the activity of the generative glands mostly disappears early. I think that most will agree with me that if we speak of pluriglandular disturbances in this disease, we shall have to assume a functional and trophic influencing of the ductless glands. The relations in tabes and progressive paralysis seem to me to be very similar. *Kraepelin* has grouped paralysis with the diseases of metabolism; to which group *Raymond* has ascribed tabes. This seems to me to be overdrawn. In the same manner we could regard the infectious diseases as metabolic diseases. Indeed it is true that in tabes and paralysis the alterations of metabolism are so prominent that at times they almost dominate the clinical picture. I refer to the losses of weight, to the marked cachexia of tabetics, to the decalcification of the bones, which gives rise to the spontaneous fractures, to the positive alimentary glycosuria that is so marked in this condition. Here too the irritative symptoms on the part of the nervous system are so fulminant, the tabetic gastric crises, the vesico-intestinal crises, the enormous hypersecretion of gastric juice, moreover the vasomotor disturbances, tachycardia, sweats, dermographism, and the trophic disturbances, abnormal pigmentations, mal perforant du pied, etc. If here I look around for symptoms on the part of the ductless glands, I find almost only the degenerative changes in the sexual glands, that has been demonstrated by *Marchand* and *others;* these may be conditioned by the syphilis, but it might also be conceived that they exist on a trophic degenerative basis. I could regard any of the other symptoms as ductless glandular, only in the sense that they might be secondary. *R. Stern* regards the basis of the fact that only a percentage of persons infected with lues become affected with metasyphilis in the vulnerability of the ductless glandular system in the mapping out [Anlage] of such persons. According to this view, the affection of these glands furnishes the impulse for the development of the tabes or the paralysis. Even though in my dissertations I arrive at a standpoint that is almost the opposite of *Stern's*, I would nevertheless recognize the ingenious conception of *Stern's* work.

I would here summarize briefly the facts arrived at from the above exposition. Even though we may be inclined to refer to functional alterations of the ductless glandular system changes in metabolism in the course of neuroses of the vegetative nervous system or in the course of nervous diseases in which manifestations on the part of the vegetative nervous system become prominent, we are not on this account justified in regarding these diseases as true ductless glandular affections. At all events it must be acknowledged that it is not yet possible to draw a clear line of demarcation between certain ductless glandular affections and the vegetative neuroses; the neurosis theory of Basedow's disease has not as yet been fully rejected, nor is the supposition that in the pathogenesis of diabetes mellitus there is the admixture of a marked component of neurosis. But sufficiently firm foundation has been built by experimental pathology, in the majority of ductless glandular affections, to justify a sharp demarcation from the vegetative neuroses, at least nosologically.

## Pluriglandular Disturbances

Proceeding from this standpoint, we now go on with a consideration of the question of the pluriglandular disturbances. Of late this question has been especially discussed in France. *Claude* and *Gougerot*, on the basis of clinical observations and certain pathologico-anatomical findings, first conceived the idea of an insuffisance pluriglandulaire. Proceeding from the observation that under circumstances certain ductless glands may become diseased simultaneously, they attempted to furnish the demonstration that in the most diverse ductless glandular diseases symptoms are found almost regularly that point to the affection of another ductless gland. The authors have found many disciples. The direction of this is characterized by the classification of *Laignel-Lavastine*. *Laignel-Lavastine* distinguishes "syndrômes pluriglandulaires à prédominance thyréoidienne, à prédominance hypophysaire, à prédominance génitale et sans prédominance marquée." *Claude* and *Gougerot* have further developed their teaching in that they point out that also conditions of hyperfunction of several ductless glands may exist simultaneously, and that not rarely conditions of hyperfunction of one ductless gland are combined in the clinical picture with manifestations of absence or deficiency of the function of another. They distinguish, of ductless glandular diseases, seven categories:

1. Syndrômes uniglandulaires avec lésion pluriglandulaire; example, classical myxedema.
2. Syndrômes pauciglandulaires; that is, predominance of the disease in one ductless gland, but distinct alteration in the others.
3. Syndrômes d'insuffisance pluriglandulaire sans prédominances.
4. Syndrômes d'hyperfonction pluriglandulaire; example, acromegaly, hyperfunction or dysfunction of the hypophysis with hyperfunction of the thyroid gland, suprarenal glands, etc.
5. Syndrômes pluriglandulaires de balancément; that is, a hyperfunction that developed compensatorily as the result of a primary falling away of the function, for example, Basedow's disease that follows a "hypoovarie."
6. Syndrômes pluriglandulaires disharmoniques; example, Basedow's disease combined with myxedema and "hypoovarie."
7. Cas d'attente à syndrômes frustes.

*Gougerot* goes still further, including the glands with external secretion in the pluriglandular syndrome; for instance, he describes: syndrome *Mikulicz*, lacrymo-parotidien avec symptômes d'hypoovarie évidente, hypothyréoïdie et hypoépinephrie probable. The disciples of *Claude* and *Gougerot* have also included the trophoneuroses. Thus *Siccard* and *Rousay*, later together with *Berkowitsch*, explain a case of Dercum's disease as insuffisance ovarothyréoïdienne. From these views *Renon* and *Delille* have drawn far-reaching therapeutic consequences, in that they propose an "opotherapie associee" in those conditions in which a trial with simple opotherapy fails. Thus the authors found that in one case of Dercum's disease ovarian substances, and later thyroidin, remained inactive, while on the contrary the combination of these two remedies was effective. A case of myasthenie bulbospinale was improved by the combined administration of ovarian and hypophysial substances, a scleroderma by thyroidin and ovarian substances, a Basedow's disease disappeared on the administration of hypophysial and ovarian substances, a case of acromegaly was essentially improved through ovarian substances and thyroidin, etc. *R. Dupuy* used polyopotherapy for the development of individuals who had remained behind or were at a standstill, and saw a striking improvement after one-half to one year's treatment. The admixture of all nosological unities goes so far that *Grasset* says: The insufficiency of a ductless gland always becomes more and more a rarity or a "création artificielle," the group of insuffisance pluriglandulaires crowds the others more and more and perhaps in time will quite replace them. With all this who does not feel the ground wavering under his feet?

I must not leave unmentioned the fact that voices, even in France, have been raised against these extreme overdrawings. *Roussy* maintains a very reserved attitude. He speaks of an ingenious hypothesis, but [that] methodical sections are as yet wanting.

The question seems to me to gain clearness if we distinguish between pluriglandular insufficiency or pluriglandular syndromes on the one hand, and multiple ductless glandular sclerosis on the other; for the existence of a pluriglandular syndrome does not signify the existence of a multiple ductless glandular disease. On the basis of what I have already written, I must assume that the pluriglandular syndrome comes about

1. Through physiological correlation.
2. Purely functionally through influencing on the part of the vegetative centers.

I have gone more intimately into the question of the latter factor in the consideration of the vegetative neuroses. As far as the physiological correlation is concerned, it seems to me that it affords no ground for a confusing of the sharply delimited disease pictures of the individual ductless glandular diseases. Let us first consider the diseases due to deficiency. That in myxedema the activity of the glands of generation is diminished or that in hypophysial dystrophy there occurs even marked degeneration of the sexual glands belongs to the disease pictures themselves. On account of this no doubt is cast on the view that in the first case the thyroid gland is the central figure of the pathogenesis, in the second the hypophysis. The disease pictures that, however, we assume as the result of a pathological correlation already belong to multiple ductless glandular diseases: I refer once again to the simultaneous degenerative lesions of the thyroid gland and the glandular hypophysis, of the thyroid gland and the insular apparatus of the pancreas, etc. The pathological correlation finds its most complete expression in that clinical picture, well characteristic in a symptomatological respect, that I have termed multiple ductless glandular sclerosis.

Undoubtedly more complicated are the relations in the hyperfunctional diseases—not so very much in Basedow's disease. Although in this condition we may acknowledge a functional increase of the chromaffin tissue, this is secondary and well enough explained by physiological correlation. That long continued oversaturation of the body with thyroid-gland secretion may give rise to disturbances of the functions of the sexual glands is not at all remarkable, only the significance of the thymus hyperplasia is as yet unclear. But on this account, not to wish to consider Basedow's disease as clinical entity seems to me incomprehensible. Sooner could acromegaly be regarded as a pluriglandular disease; this is not new, however, but was already mentioned by *Pineles* in his classical work. In addition to hyperplasia of the hypophysis, we not rarely find symptoms of Basedow's disease, in the later stages eventually symptoms similar to myxedema, also to diabetes, and in the most cases, as is known, premature disturbances on the part of the glands of generation, which may, however, be sometimes preceded by temporary increase of their function. Of late years too have been issued reports as to hyperplasia of the suprarenal cortex; briefly, in acromegaly there comes about a pluriglandular hyperplasia of the ductless glandular system, which mostly is rapidly followed by a degeneration and exhaustion. This, however, likewise belongs to the disease picture of acromegaly, and on this account we would hardly be likely to confuse a Basedow's disease with an acromegaly.

These pluriglandular disturbances are found much more pronouncedly in many cases of gigantism. Here the hyperplasia would seem to be a partial manifestation of an abnormal predisposition to growth of the entire body.

Concerning the therapeutic results of opotherapie mixte, that have been hailed with such enthusiasm, they must be regarded with much scepsis, especially in so far as they are concerned with the trophoneuroses of the vegetative nervous system. However, I do not wish to deny the justification for this therapy in combined diseases due to absence [Ausfall].

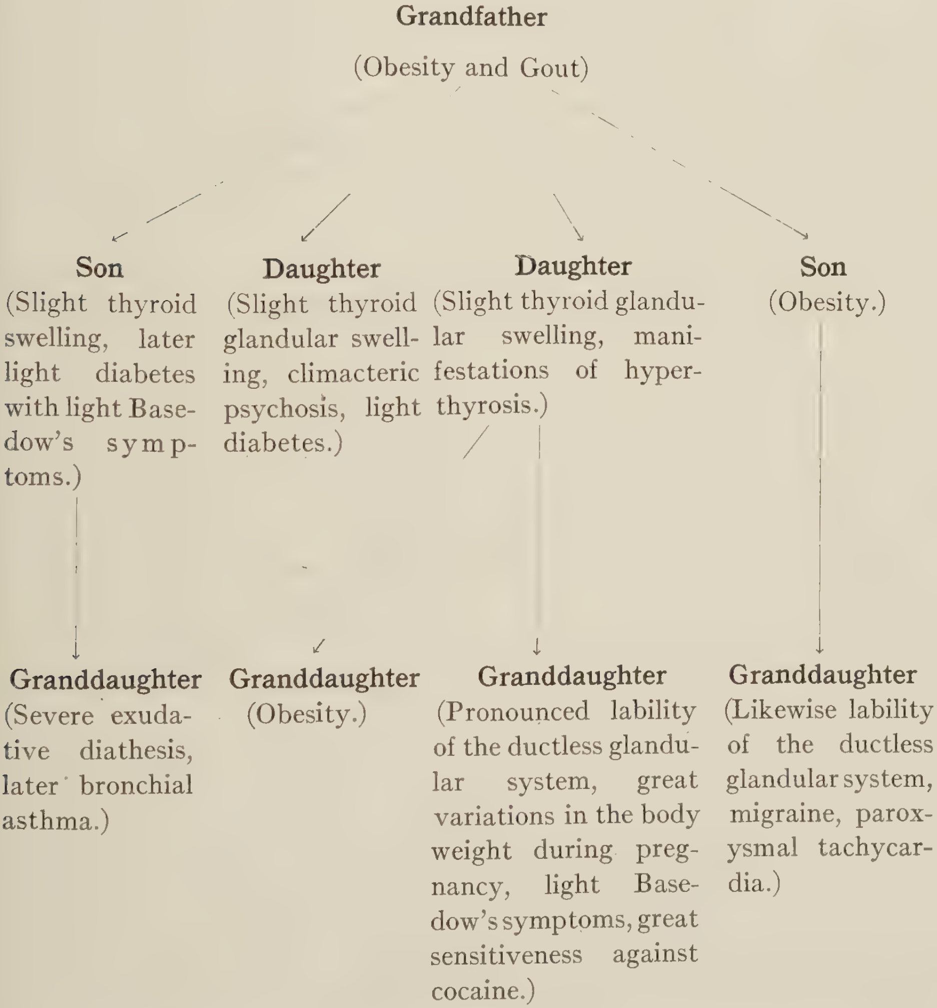
Desirable seems to me a sharper delimitation of the ductless glandular diseases, not only from the vegetative neuroses, but also from certain **vegetative disturbances.** The regarding of chondrodystrophy as a ductless glandular disease has been practically done away with. Mongolism is regarded to-day as a product of degeneration, in which a thyogenic component is associated at most. Lately true dwarfism has been regarded as a disease due to deficiency of the hypophysis, a view that will hardly meet with general acceptance. Most obstinate are the attempts to obtain a place among the ductless glandular diseases for true infantilism. In true infantilism the organism, on account of a damage in fetal or postfetal life, does not progress beyond the child stage of development. In this remaining behind, the ductless glandular system participates, as well as the central nervous system and every other organ of the body. There are, however, no indications that the ductless glands functionate deficiently; which dictum holds also for the sexual glands—these functionate, but only as in the child organism; if they were not to functionate, the genitalia and dimensions of the body would be eunuchoid, but not infantile.

## The Ductless Glands and Constitution

After the above attempts to delimit the ductless glandular diseases from the disease groups that are related to them, I would add a few remarks as to the *significance of the ductless glandular system for the total constitution of the body*. *Martius* says "die Gesamtkonstitution ist die Summe der Teilkonstitutionen" (the total constitution is the sum of the partial constitutions). I might suppose that from the study of the physiology and pathology of the ductless glandular system we have obtained a deeper insight into one of these partial constitutions. At all events we must not accept the ductless glandular system for itself alone, but must regard it as a constitutional component; the ductless glands as vegetative organs together with the nervous system regulating their functions. *Wunderlich* distinguishes a strong, an irritable, and a lax constitution. This classification seems also to apply to those factors of the general constitution whose differentiation we are at present concerned with. We can divide individuals into those with *stabile*, those with *debile* and those with *labile* vegetative nervous systems and individuals with *stabile*, *debile* and *labile* ductless glandular systems.

The certain degree of autonomy that is an attribute in general of the ductless glandular system has as a sequel the fact that the corresponding partial constitutions may occur separately; the intimate relations that exist between both systems would lead us to expect, however, that they are to be very often found united in the same individual or that where one is present the other is at least suggested. As the hereditary factor is very prominent in both, we find them in the most diverse variations and combinations in members of the same family. In individuals with a predisposition to a debile vegetative nervous system there develop, under the demands that life makes on the organism, an asthenia of the vegetative organs with general enteroptosis, sluggishness of evacuations, anomalies of the secretion of gastric juice, depressive mental attitude, in short the features that are an expression of *Stiller's* asthenia. In the individuals predisposed to a labile vegetative nervous system, readily accessible to irritations, there exists a tendency to neurasthenia, hysteria, and the vasomotor-trophic neuroses. It seems to me that this classification is suitable in the smallest detail too for the ductless glandular system. The ductless glandular debile individuals are those in whom there is not only a small functional breadth, but perhaps also a certain tendency for certain diseases, especially for infections, or a slighter resistance against alcohol or against certain toxins that may proceed from a focus of infection somewhere in the body. To me the most interesting are the ductless glandular labile individuals. These are individuals who several times in the month show extraordinary variations in the body weight, or those in whom the thyroid swelling that occurs normally during pregnancy leads to slight manifestations of Basedow's disease, or those in whom a strong emotional excitement calls forth temporary glycosuria, or perhaps those in whom slight symptoms of acromegaly occur during pregnancy; or women in whom exist marked dysmenorrheic distresses. In this group are always to be found too some symptoms that point to an especial lability of the vegetative nervous system. I need not attempt the description of the stabile individuals. They are those with an enviable equilibrium of their vegetative functions, their metabolism and their psyche.

The relationship of both the disease groups is also shown, as has already been mentioned, in the fact that they sometimes occur combined or alternating in the members of one family. I here submit an example:



**Grandfather**
(Obesity and Gout)

**Son**
(Slight thyroid swelling, later light diabetes with light Basedow's symptoms.)

**Daughter**
(Slight thyroid glandular swelling, climacteric psychosis, light diabetes.)

**Daughter**
(Slight thyroid glandular swelling, manifestations of hyperthyrosis.)

**Son**
(Obesity.)

**Granddaughter**
(Severe exudative diathesis, later bronchial asthma.)

**Granddaughter**
(Obesity.)

**Granddaughter**
(Pronounced lability of the ductless glandular system, great variations in the body weight during pregnancy, light Basedow's symptoms, great sensitiveness against cocaine.)

**Granddaughter**
(Likewise lability of the ductless glandular system, migraine, paroxysmal tachycardia.)

I would consider it probable that such family trees are not at all hard to find, at least they do not occur isolated, but readily could be traced in the family trees of families with diatheses.

This affords me the opportunity of saying a few words with regard to the significance of the ductless glandular systems for the **diatheses.** According to *W. His* we understand by diathesis an individual, congenital, and often inherited condition, which consists in the fact that physiological stimuli call forth an abnormal reaction and that conditions of living, that are borne without harm by the majority of the race, call forth conditions of disease. The circumstance that in the great group of arthritic diatheses, as also under the diatheses of pediatrics and dermatology, there are found conditions that we regard as vegetative neuroses shows that the vegetative nervous system has a prominent place here. *Rapin* sees also in a familial and inherited lability of the nervous system the connecting link between the individual diatheses. In this connection we must turn our attention to the ductless glandular system. Actually we find that diabetes and obesity play a prominent part in the great group of arthritism. The connection between gout and the ductless glandular system is, of course, at first hand as yet quite unclear. In the pathogenesis of the spasmophilic diathesis we must, even with the use of the utmost reserve, ascribe some significance to the parathyroid glands. Also for the genesis of lymphatism the observations that status lymphaticus is regularly associated with hypoplasia of the chromaffin tissue cannot be quite without significance. For the predisposition to the dermatoses the processes in the sexual sphere are of importance, as *Bloch* emphasizes; for just at the transitional periods, at puberty and at the climacteric, certain dermatoses are very common, and others, like favus or trichophytina, disappear with the beginning of puberty. Here the ductless glandular system exerts a certain influence on the natural immunity.

A very much older observation concerns the known inclination of diabetics for furunculosis, and the great vulnerability of their tissue. This may be shown experimentally: it is known that after extirpation of the pancreas it is not easy to obtain a reactionless healing of the laparotomy wound. *Bloch* infected the skin of dogs with yeast before and after the extirpation of the pancreas and found that the affection was much worse in the dogs without a pancreas. The fact in itself cannot be gainsaid, but as yet we are without any deep insight into the nature of this disease susceptibility.

As may be gathered from the elucidation of the idea of diathesis through the summarizing "Referate" (references) of *His*, *Pfaundler*, and *Bloch*, we are dealing in the diathesis not with sharply circumscribed disease pictures, but with an exceedingly manifold disease susceptibility resting on as yet hard to define factors; alterations in the function of the ductless glands constitute only one of such factors; in a theoretical sense I would not, however, estimate this factor as of slight importance, for if we see in the interest that physicians have taken in the question of diathesis a sort of resurrection of the old humoral pathology, and if we seek in an altered blood admixture and the consequent changing of the tissues the cause of the tendency of the disease, we find that the little that the study of the ductless glandular diseases has afforded for the knowledge of diathesis has up to the present first furnished an idea as to the genesis of this alteration of the blood admixture and the tissue changes that follow it.

Finally a few words as to **senility.** *Horsley* first pointed out that the alterations of the skin and other tissues that occur in old age, especially the increase of the connective tissue, have a certain similarity with those that occur after extirpation of the thyroid gland, and that on the other hand localization of the fat deposits in old age is similar to that in eunuchoidism.

In a detailed study *Lorand* has upheld the idea that the degeneration of the ductless glandular system is chiefly the cause of senility. I would not concur with this, so far as physiological old age is concerned, but believe much more, as does also *Ewald*, that the ductless glandular system like every other organ participates in the involution of old age. There is on the other hand a pathological old age, setting in prematurely or associated with distinct accentuation of the cachexia. The premature senility which develops in most of the diseases due to giving out of function, and especially in multiple ductless glandular sclerosis, makes intelligible to me the fact that degeneration in the ductless glandular system may be one of the causes of pathological age.

### Addendum

With regard to what has been written *in toto*, it may be said that the author's views respecting the grouping, the reciprocal action, etc., of the ductless glands, and their effects on the various organs and systems of the body, are sound. On the whole they seem to be somewhat in advance of the general conception in America of the purport and scope of the ductless glandular apparatus, in so far at least they are distinctly definite. There seems to be a tendency among some recent investigators to claim too much for the ductless glandular system and to jump to conclusions, attributing effects to the system of endocrinous organs that might just as well be explained by metabolic processes that are general, or that are part of constitutional factors at least one step removed from purely internal secretory activities.

The author's chapter on ductless glands and constitution has the tendency to counterbalance this drift. Here the various ductless glandular constitutional states are considered as part of a "total constitution," which is made of factors that mutually influence each other, including the ductless glandular system. If to the modern mind such an attempt to revive the idea of "constitution" and its sister conception "diathesis" savors too much of the old humoral pathology (which by the way in its serological form has led or will lead to a later chemical aspect of the subject which will perhaps be all-embracing so far as relation between cell and tissue juices is concerned), it must not be forgotten that "constitution" itself represents but one factor of a far more extensive subject—heredity, a subject that in its last analysis resolves itself again into factors that are mechano-chemical, and perhaps is part dependent on the activities of just these ductless glands.

The Abderhalden reaction has already furnished results with regard to the reciprocal activities of the various ductless glands. To the editor's mind it would seem that the importance of the significance of the Abderhalden reaction (in general, not simply the pregnancy test) has not as yet been sufficiently realized, at least in this country. That its basic principle, the formation of ferments—chemical substances—for the splitting up of alien or other proteids, as a matter of "Abwehr," defense, is a biological phenomenon at the basis of life itself, and it will be indeed strange if this principle, capable as it is of exact chemical demonstration, does not yield practical results far in advance of present indications.

The matter of "Abwehr" leads us to two other so-called discoveries of recent years—the Freudian theory of the genesis and treatment of hysteria and allied neuroses and the so-called "kinetic theory" of *Crile.* Of these the latter merits discussion here because of its direct relation with the ductless glandular diseases, and the former because of the relation of the various neuroses (and even psychoses) to the ductless glandular system. It is a pity that *Crile* has not as yet (September, 1914) published the results of his experiments *in toto* and in detail, as much of what he claims for his theory (based as it is on painstaking examination of, among other objects, 40,000 nerve cells) seems to be substantiated by older and more recent theories of the central nervous origin of such ductless glandular conditions as Basedow's disease and diabetes mellitus. (*Crile* will be mentioned again under Basedow's disease.)

With regard to *Freud*, I have been anticipated in what I wished to say by *Cushing;* as I consider the matter very well expressed by that author, I shall quote *in extenso* passages from one of his works:

"The pituitary body and the germinal glands appear to be protagonists. Hypophysial insufficiency and a lowering of the activity of the reproductive functions go hand in hand, and in some of our examples of hypoplasia, glandular feeding has unquestionably led to a restoration of potentia. The reverse is probably also true, for, as stated, a libidinous tendency often accompanies states of secretory hyperplasia, and certain experiments undertaken with *Dr. Emil Goetsch* have indicated that feeding pituitary extracts to preadolescent animals leads to a precocious ovulation and spermatogenesis. These observations, coupled with the knowledge that secretory discharges from the hypophysis may be elicited through the sympathetic nervous system, suggest that the liberation of a chemical messenger may account for the recognized effect of the emotions upon the sexual sphere."

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"It is plain that the two intracranial glands, hypophysis and epiphysis, normally exercise a remarkable influence not only upon the nutrition and skeletal growth, but also upon the sexual sphere, and it is not a matter for surprise that in the presence of a definite pathological derangement of either of these structures which dates from childhood, mentality should be so modified as to produce peculiar if not defective individuals when measured by the standard of the average.

"With this conception we may find some physiological or pathological basis for what is regarded by many as a psychotherapeutic phantasy; for the various neuroses and asthenias may arise primarily as the result of some disturbance of internal secretion which proves the way for the dreams, symbolisms, neurograms and other ascrotical manifestations dissected by the psychoanalyst. If therefore we are to swallow the Freudian doctrines whole—a difficult morsel for many—and are to interpret hysteria and the psychoneuroses solely as the resultant of early mental conflicts and compromises between the libido and its repressions, it will be easily seen that any secretory duration which on the one hand excites, or on the other diminishes, sexual activities must be an important element in modifying the terms affecting the ultimate compromise.

"We have of course been considering extreme examples, but it is quite probable that the psychopathology of everyday life hinges largely upon the effect of ductless gland discharges upon the nervous system. This is particularly worthy of consideration in the study of child psychology in its relation to puberty and adolescence, especially in those individuals in whom there is some underlying, possibly inherited, functional deviation in the chemistry of the internal secretion. At any age, however, in the presence of some ductless gland irregularity, which in chemically speaking more stable individuals would be transient, may produce secretory disturbances, characterized by more or less chronicity."

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"It is hoped that some serological test, possibly in the direction of Abderhalden's investigations on the serodiagnosis of pregnancy, will serve to give us a chemical reaction of diagnostic value, at least, for states of overactivity of individual glands . . . and we possibly may come to attach an importance to the findings of pathological serology far greater than that which in the past we have given to the cytological changes shown in the microscope."

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It was part of the philosophy of the ancients to explain change in matter as due to the "love" of the elements. We still speak of chemical affinities. Nowadays we resolve love into its chemical constituents. All of which makes not one whit less, but rather much more wonderful, the phenomena manifested by the various bindings together of atoms.

Thus is the Freudian theory placed on a materialistic basis with regard to the genesis of certain of the epiphenomena of some of the neuroses. That the underlying factor of heredity governs here the constitution, predisposing either the ductless glandular or the nervous factor or both to abnormal action, there can be no doubt. One thing at least we may be assured of: without internal secretion, no thoughts. The fact, however, that the nervous tissue seems to be especially susceptible to the influence of the internal secretions of what is ordinarily known as the ductless glandular system does not preclude its influencing by products of cellular activity elaborated in the course of diseases that have nothing to do with the ductless glandular system (I am indebted for this idea to remarks by *McCarthy*, in an extempore address) or in which, as in the infectious diseases, the ductless glandular system is influenced only indirectly. This subject last mentioned, that of ductless glandular affection in the course of infectious disease has been taken up especially by *Sajous*, to whom we are indebted so much for attracting our attention to the importance and scope of ductless glandular affections.

What is especially noticeable in the ductless glandular diseases is the employment of chemical substances or glandular extracts in their diagnosis—a use for these substances or extracts that independently of the ameliorative effects is perhaps new in the art of diagnosis, and that may perhaps mark the beginning of a new science, that of pharmacodiagnosis.

*Crile* (*G. W.*). The kinetic system, Cleveland M. J., Vol. XII, No. 4, October, 1913, p. 665, associated with which is:

*Hitchings* (*F. W.*), *Sloan* (*H. G.*), and *Austin* (*J. B.*). Laboratory studies of the brain and the adrenals in response to specific stimuli, Ibidem, pp. 684–691.

*Crile* (*G. W.*) and *Lower* (*W. E.*). Anoci-association. W. B. Saunders Co., Phila., 1914.

*Cushing H.* Psychic disturbances associated with disorders of the ductless glands. Am. J. Insanity No. 5, 1912, special number, pp. 965–990.

*Sajous* (*C. C. de M.*) Among other articles: Hypoadrenia as a cause of death in infections and its treatment. Monthly Cyclopædia and Medical Bulletin, Vol. IV, 1911, pp. 725–729. Also his Internal secretions and the principles of medicine, 5th edition, Phila., F. A. Davis and Co., 1912.

# CHAPTER II

## THE DISEASES OF THE THYROID GLAND

**Anatomy and Embryology.**—The thyroid gland of man has the shape of a butterfly. Two of the lobes lying on the lateral surfaces of the trachea and larynx are joined together by the isthmus, which is sometimes prolonged for a certain distance superiorly as the so-called processus pyramidalis. The weight of the thyroid gland in the adult approximates 36–50 gm.

The isthmus is developed from an unpaired evagination from the ventral wall of the head-gut cavity. In many of the lower animal classes the connection with the head-gut—the ductus thyroglossus—is retained. Here the thyroid is a gland with external secretion. In the higher animal classes the ductus thyroglossus obliterates early. Concerning the development of the lateral lobes opinions to-day are still divided. It is safe to say that a portion of the lateral thyroid gland rests are developed through evagination from the median rest. It is further certain, according to the investigations of *Erdheim* and *Schilder*, that the so-called postbranchial bodies, that originate from the ventral wall of the fourth branchial pouch, can give rise to thyroid gland tissue, for in the cases of thyroaplasia in which the medium rests of the thyroid remain rudimentary, the indifferent rests of these bodies regularly contain some thyroid gland follicles. It is therefore only uncertain to what extent under normal conditions the lateral rests of the thyroid gland take part in the formation of the lateral lobes. To aid the better comprehension of the subject, I subjoin the accompanying sketch taken from the work of *Maurer* in which is shown the development of the parathyroid and the thymus glands.

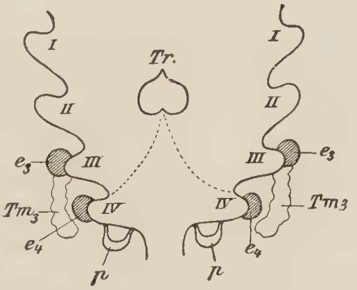

FIG. 3.—*Tr* = Thyroid; *I*, *II*, *III*, *IV* = pharyngeal pouches; $e_3e_4$ = rudiments of the parathyroid glands; *p* = postbranchial bodies; *Tm* = rudiment of thymus.

The rudiments of the thyroid wander downward with the heart. Along the entire tract from the root of the tongue to the aorta may be found cut-off portions of thyroid glandular tissue, accessory thyroids, which may give occasion to the formation of abnormally situated goiters (tongue goiters, retrosternal goiters, etc.).

The thyroid is remarkably well vascularized. It consists histologically of follicles lined with cubical or cylindrical epithelium, which for the most part are filled with colloid. This contains the specific secretion, which, according to the need, gets into the circulation, probably through the lymph paths. *Fr. Kraus* therefore designates the thyroid as a reserve or storage gland. The thyroid is signalized by an especially high contents of iodine; in the formation of the specific secretion the iodine is bound to an albuminous body thyroglobulin.

We may divide the **diseases of the thyroid gland** into those which for the most part do not especially restrict its functions, but produces local symptoms, chiefly, and those the principal symptoms of which depend on the alteration of the internal secretory function. To the first belong certain forms of the **goiters,** the **tumors** and the **inflammations.** The goiters are discussed in the chapter on the cretinic degeneration.

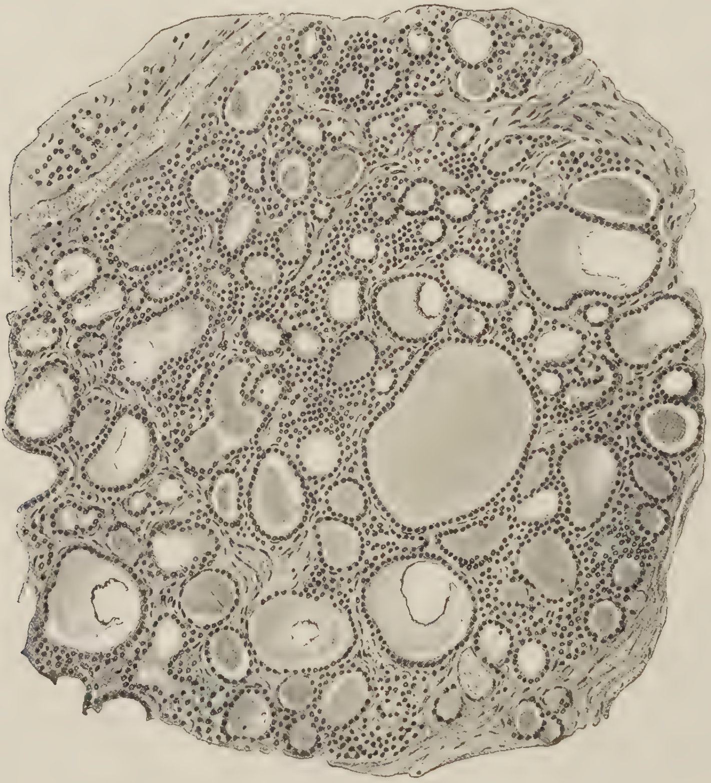

Fig. 4.—Normal thyroid gland with colloid formation.

**Tumors of the Thyroid Gland.**—Among the tumors are found most commonly adenoma, carcinoma and sarcoma. The simultaneous occurrence of sarcoma and adenoma in the thyroid gland has been reported (*Saltykow* gives the literature). The tumors mentioned all show a great tendency toward the formation of metastases. In carcinoma bone-metastases are especially frequent, especially in the bones of the skull and in the sternum; in sarcoma, metastases are frequently found in the lung. The metastases of adenocarcinoma of the thyroid gland contain a not inappreciable amount of iodine. *Gierke* reports two cases of carcinoma of the thyroid with metastases in the vertebral column. In the case of *Ewald*, the highly decomposed primary adenocarcinoma of the thyroid was iodine free; the metastases in the lungs and lymph-glands contained iodine. The decision as to whether an adenoma of the thyroid is malignant or benign is often very difficult (*v. Eiselsberg*). Microscopically metastases may appear as gelatinous goiters, and yet the very presence of metastases may in itself be regarded as the sign of malignancy. In addition, not rarely the metastases show microscopically a formation similar to carcinoma.

On account of the proximity to many important organs (trachea, esophagus, sympathetic, vagus, etc.), tumors of the thyroid not infrequently cause very manifold local manifestations, that will not be discussed further at this place. They may also give rise to alterations in the thyroid function. Symptoms of deficiency [of secretion] are relatively rare, and it may then happen that the symptoms of myxedema retrogress when metastases develop (*v. Eiselsberg*) or when accessory thyroids begin to grow. This may even occur when the metastases have become degenerated carcinomatously. Indeed *v. Eiselsberg* found in the metastases in such a case follicles still filled with colloid. Further, not so very rarely do malignant tumors of the thyroid gland take on the characteristics of Basedow's disease. *Sattler* has collected sixteen such cases, of which eleven were carcinomata, and three sarcomata, while in two the character was not determinable. Indeed the Basedow's symptoms may not appear until just at the time that the metastases develop (*J. Löwy* has collected the literature). We find therefore that malignantly altered thyroid gland tissue may not only affect the normal function, but, when proliferation is rapid, may even lead to hyperfunction. The interpretation of the symptoms of Basedow's as hypothyrosis (*Minnich*) is not to be regarded as correct.

**Inflammations of the Thyroid Gland.**—We differentiate between thyroiditis and strumitis. The first is very much rarer, as apparently the normal thyroid shows little tendency for inflammatory processes, which has also been determined experimentally on animals. Also in thyroiditis, as *Jeanseline* mentions, is the termination in suppuration much rarer. A light inflammation of the thyroid is very often an accessory phenomenon of acute infections (*Roger* and *Garnier*, *Kashiwamura*, *de Quervain*, *Sarbach*, and *others*). The histological alterations, which consist in epithelial desquamation and disappearance of the follicles, hyperemia, etc., may be not inappreciable after scarlet fever and variola, and also after other infectious diseases. Thyroiditis is not uncommon in the early stages of syphilis (according to *Engel-Remiers* in 56 per cent. of cases). Slight sclerotic processes are often present in tuberculosis and in severe alcoholism. Severe inflammatory processes in the thyroid have been observed after typhoid fever, variola, influenza, malaria, puerperal processes, etc.; especially, however, after angina and acute articular rheumatism. A detailed summary of the literature is that by *de Quervain.* The primary form of acute thyroiditis which does not go on to suppuration, was first described by *Mygind* and more recently by *de Quervain* in a very thorough report. The beginning for the most part is sudden; with evident general symptoms and fever the thyroid gland becomes swollen, and local symptoms of pressure may be obtained. Then severe pains radiating to the ear and throat make their appearance, the climax of the clinical manifestations is for the most part rapidly arrived at, and quickly, or more or less slowly (lytically) all phenomena subside. The histologic picture of the thyroid gland is in many respects similar to that of the Basedow thyroid. Nothing is known as yet as to the causative agent. Therapeutically quinine and salicylic acid, according to *de Quervain,* are the drugs to be considered; we must operate only when distinct fluctuation is present.

Not infrequently the inflammations of the thyroid gland lead to pronounced disturbances of function. In a case of *Reinhold's* symptoms of Basedow's appeared after influenza, and in a case of *Gilbert* and *Gastaigne's* in the convalescence of typhoid fever. Worth mentioning is a case of *de Quervain's* with recurring articular rheumatism and parallel symptoms of a slight thyroiditis and a Basedow's. *Apelt* reports a case of suppurative inflammation of a goiter of the tongue. After three days a thyroiditis made its appearance, then there developed a Basedow's which later disappeared almost entirely. Also the clinical primary forms may be associated with similar manifestations. In a case of *Breuer's* a typical Basedow's developed immediately after an acute thyroiditis. As *Möbius* has already pointed out, we cannot deny for these observations a certain significance in the pathogenesis of Basedow's disease.

Chronic inflammatory sclerosing processes commonly lead to myxedema (see later).

I may not leave unmentioned that administration of iodine serves to increase the acute thyroiditis (*Dunger*). In the case of *Himmelheber* the thyroiditis appeared immediately after a gynecologic operation; with high fever, tachycardia, acute cardiac dilatation and with delirium, there occurred a rapid disappearance of the thyroid swelling, which *Himmelheber* ascribed to the iodine absorbed from the iodine catgut.

The *second* group of diseases, those in which the *internal secretory activity* of the thyroid gland stands in the foreground, may be divided into diseases associated with increase of function and those with diminution or lack of function. I begin with the first, as they are better adapted to give an idea of the normal function of the thyroid gland.

### (a) Morbus Basedowi [Basedow's Disease]—Hyperthyrosis

*Synonyms.*—Graves' disease, Morbo di Flajani (Flajani's disease), goître exophthalmique [exophthalmic goiter], [Parry's disease].

**Historical.**—In the year 1840, *v. Basedow* first thoroughly described three cases of the disease named after him. Of his precursors, is especially *Graves* to be mentioned, who in 1835 described cases of the disease and brought it into close relationship with hysteria. Since the time of *v. Basedow*, the views as to this disease have undergone great changes. The French school regarded it as neurosis, *Möbius* first in 1886 assumed an abnormally increased activity of the thyroid gland as the cause, and pointed out the opposition that exists between this disease and myxedema.

**Definition.**—By *Basedow's disease* we understand to-day a disease *which is brought about principally by the abnormally increased activity of the thyroid gland.* This is almost always accompanied by an *enlargement* and *increased vascular engorgement* of the thyroid gland and leads eventually, *through the local symptoms conditioned by the enlargement* to a great number of very *manifold manifestations*, of which especially the *tachycardia*, also the *well-known eye symptoms, the tremor, and the increase in metabolic* processes are the most important. The most of the manifestations are to be explained by a *heightened condition of excitement of the vegetative nerves.* Regularly and very manifold is the, indeed for the most part, probably *secondary, involvement of other glands of internal secretions.* The syndrome that results depends therefore not upon the *degree of hyperfunction*, but on the *constitution of the individual affected*, that is, on the reaction capability of this ductless glandular apparatus. *The cause of hyperthyrosis is not at present known. The possibility* exists that it is conditioned centrally, and that many symptoms of Basedow's are coordinate with the hyperthyroidism.

**Occurrence.**—Basedow's disease is rather irregularly distributed. A careful collection as to its occurrence has been made by *Sattler*. The most of the investigations concerned with this subject founded in part on a very great observation material, agree that the classic form of Basedow's disease is relatively of rare occurrence in regions where goiter is endemic. I mention only the contributions of *H. Bircher, Fr. Kraus* and *W. Scholz*. In Germany, for example, typical cases of Basedow's disease are very much commoner in the northern parts; they seem to be especially numerous in the Russian East-sea provinces (*Kroug*). It is very much more common in the female sex than in the male. In *Sattler's* compilation 3210 of the 3800 cases were females. It is not very common in childhood (according to Sattler out of 3477 cases, only 184 were in children under fifteen years of age). Basedow's disease in sucklings appears to be very rare. *White Clifford* has reported a case. The mother of the child had also previously given birth to a child affected with symptoms of Basedow's. In the case described there were present exophthalmus and a struma, that microscopically gave a picture very similar to that of a typical Basedow's struma. Familial occurrence of Basedow's disease is not at all uncommon. *E. Frey* reports a family of five persons, of whom four suffered with Basedow's disease. *Österreich* reports likewise a family in whom ten members were affected with Basedow's disease. In the familial type we find not rarely much mitigated hyperthyroses or hypothyroses. In addition occur neuroses of the vegetative nervous system, diabetes mellitus, and even psychoses. *Grober* publishes the family tree of such a family.

Finally it should be stated that the disease is met with in animals (dogs, cows, horses), in isolated cases.

**Symptomatology.**—The pathologic alteration may develop in a previously normal thyroid gland or in a **thyroid gland** degenerated into a goiter. The thyroid gland increases in volume, is then of soft elastic consistence, through dilatation of the blood-vessels, also through new formation of blood-vessels it becomes very vascular, and under circumstances shows expansive pulsations and frequently also variations in volume, paralleling the phenomena of Basedow's disease; in many cases the apparently not enlarged thyroid may become palpable through voluntary increase of the intrathoracic pressure (*Fr. Kraus*). In acute cases the swelling of the thyroid may appear over night and even lead to difficulty in breathing. It can subside just as suddenly (*Trousseau, Möbius, et al*). On the application of a stethoscope applied to the gland, we can for the most part hear vascular murmurs synchronous with the heart action (*Guttmann*). The hand laid on the gland feels a distinct thrill; we can diminish the size of the gland by pressure. The enlargement of the gland is a very common symptom, yet there certainly do occur cases with distinct manifestation of hyperthyrosis, in which the enlargement of the thyroid gland is barely demonstrable. With longer duration of the disease, the consistence of the gland becomes firmer.

The *microscopical examination* shows in addition to increased vascularization, rich new formation of epithelial plugs and glandular acini which later are often well filled with desquamated cells; in addition there are accumulations of lymphoid cells (*Gibson, Greenfieldt, F. Müller, Lubarsch, et al*). Other authors (*Farner* and *others*) find less typical alterations, although *Askanazy* points out correctly that the aberrant findings come from goitrous districts; it may therefore, be assumed that in these cases the alterations of *Basedow's* have developed in thyroids that are already degenerated. *Kocher* designates the typical Basedow struma as a struma hyperplastica parenchymatosa telangiectodes; it ordinarily contains no colloid, and for the most part is poor in iodine.

Among the **cardiovascular** symptoms, tachycardia stands in the foreground. For the most part there exists in addition, an especial lability of the pulse. It may happen that on complete rest the pulse lies only slightly above the normal, while slight psychic emotions or physical movements sends it up unusually high. In addition there exist increased strength of the heart action, and cardiac palpitation. The patients feel the heart beat "up to the throat." The cardiac impulse is then increased and broadened, and the thoracic wall is strongly agitated. Very often broadening of the cardiac dullness occurs, depending more commonly on cardiac dilatation than on hypertrophy. Frequently there are accidental systolic murmurs. All manifestations on the part of the heart show great variations that parallel the remainder of the manifestations of the course of the disease.

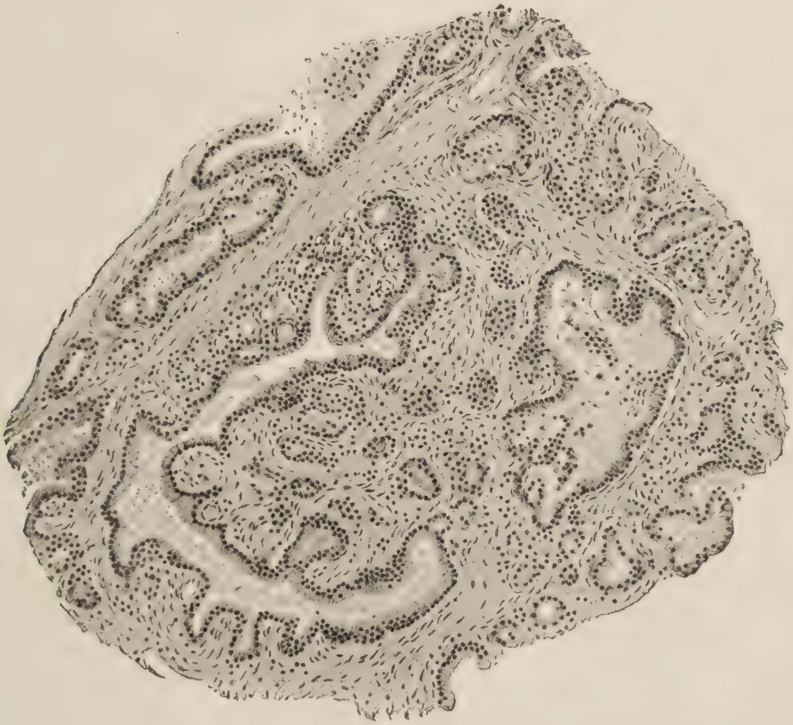

FIG. 5.—Basedow struma.

In the fully developed form of the disease the arteries of the gland often pulsate very strongly, a phenomenon that gives these cases their own characteristic feature. Especial cases may even go as far as a penetrating venous pulse in the thyroid gland or to a pulsatory shaking of the head (*Musset's* sign) or to choroid pulse (*Becker*). Also there have been observed marked beating of the abdominal aorta, hepatic pulsation, and splenic pulsation (*C. Gerhardt*). In opposition to increased heart action and the stormy pulsation in the neck the radial pulse is often small and weak and the blood-pressure not raised or even slightly diminished (*Spiethoff*, *Donath*). Heightening of the blood-pressure is relatively rare. There occurs then an abnormal fall from center to periphery (*Fr. Kraus*) which is explainable by the abnormal laxity of the tonus in the peripheral vessels. Even the earlier observers (*Graves*, *Stokes*, *Hirsch*, *Trousseau*, *et al.*) noticed this opposition between the increased cardiac activity as evinced on the part of the heart and the vessels of the neck, and the relatively slight filling of the peripheral vessels. To the slight tonus of the peripheral vessels testify also the often observable reddening of the face, the ears, the tips of the fingers and the nail matrices (*A. Kocher*).

So much for the clinical observation. Experimental investigations on the action of the thyroid gland secretion upon the cardiovascular apparatus are very numerous, but an agreement among them has not as yet been obtained. *Oliver and Schäfer*, *Fenyvessy*, *Haskovec*, and *others* found after intravenous administration of juice of thyroid gland, sinking of the blood-pressure and showing of the pulse. Other observers found no action or acceleration of the pulse-rate. The different species of animals behave differently. *v. Cyon* found that on the cat iodothyrin acted tonus increasing on the vagus and the depressor. *v. Cyon* and *Oswald* found the same true of iodthyroglobulin, while iodine-free thyroglobulin is inactive. Also *Asher* and *Flack* found an increase of excitability of the depressor nerve. *v. Fürth* and *Schwarz* consider the depressor action of the extract not specific for the thyroid gland, but attribute it to the cholin contained in the extract. The differences in the results are to be explained by the fact that on the intravenous administration of thyroid gland, substances that influence the cardiovascular apparatus are also introduced that have nothing to do with the thyroid. According to the investigations of *Falta*, *Newburgh*, and *Nobel*, the feeding of thyroid gland produced in most cases an increase in the fall of blood-pressure from center to periphery, as one observes in Basedow's disease. Tachycardia is present, the blood-pressure taken at the brachial remains the same (blood-pressure measurement according to *Rocci*) and fall of the blood-pressure in the periphery (blood-pressure measurement according to *Gärtner*).[1] On the administration of large doses of thyroidin there results a significant fall in the blood-pressure (*Pilez*). By the heightening of the fall is the velocity of the circulation increased, which best corresponds to the increased oxygen requirement.

The tachycardia is a result of the irritation of the accelerator, and the slight tonus of the peripheral vessels is a result of irritation of the vasodilator; the dilation of the thyroid-gland vessels is the result of the irritation of the depressor nerve, as irritation of the root of the depressor nerve calls forth an increase on the blood-pressure in the thyroid (*v. Cyon*). Also *Asher* and *Flack* found that the excitability of the depressor nerve is increased by the internal secretion of the thyroid gland. The increase of the blood stream favors the increased output of secretion and thus a circulus vitosus is established. Perhaps also a secondary increase of the activity of the chromaffin tissue or a greater sensitivity to adrenalin of the organs supplied by sympathetic nerves is bound up with the cardiovascular symptoms (tachycardia). The facts are that on the simultaneous administration of thyroid gland secretion and adrenalin, action pulses may also be produced in animals (*Kraus* and *Friedenthal*), the origin of which action pulses *v. Cyon* attributes to a simultaneous irritation of the vagus and sympathetic, and that according to *Asher* and *Flack*, the thyroid-gland secretion may increase the activity of adrenalin.

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[1] An exception to this is shown only by diabetics, who show an increase in blood-pressure (see chapter on pancreas).

The **eye symptoms** may be expressed in different degrees of intensity. Often there is only a slightly heightened glitter of the eye, and only on very exact examination do the existence of alterations show; in other cases occur those striking alterations that *Möbius* compares with those of the facial expression of intensest terror.

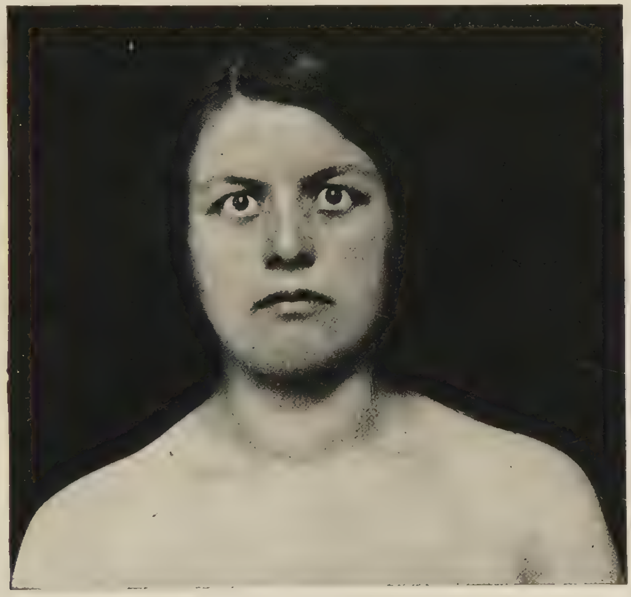

FIG. 6.—Gaping of the palpebral fissures in Basedow's disease.

As an example I shall quote the following case:

*Observation I.*—Anna K., twenty-six years old. For about two months cardiac palpitations, conditions of excitement, pains in the cardiac region, sweats, tremor and enlargement of the neck.

The width of the palpebral fissures is plain. Protrusion slight, rare blinking, thyroid diffusely enlarged, weakly elastic vascular murmurs, tachycardia up to 361 [sic.][1], blood-pressure (*Riva-Rocca*) 100. Increase of temperature up to 37.7 C., alimentary glycosuria negative.

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[1] 361 in the German edition—probably an error for 136.—*Editor.*

In many cases the development of the eye symptoms comes about very gradually. In other cases, the terrifying alterations may develop in a few days, indeed over night. We should distinguish between protrusion and widening of the palpebral fissures. In fully developed cases both symptoms are for the most part really present together. The protrusion of the eyeballs is well seen in the accompanying illustration.

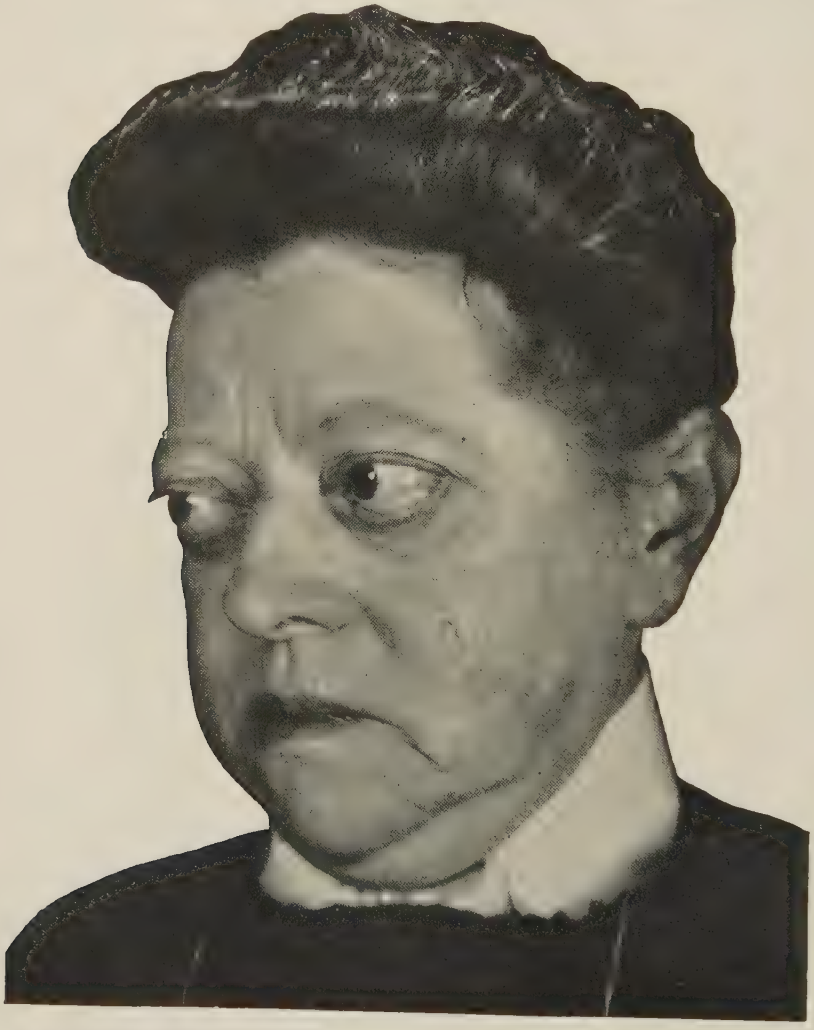

FIG. 7.— Protrusion of the globes in Basedow's disease.

*Observation II.*—K. I., fifty years old, the morbus Basedowi has lasted about ten years, tachycardia, sweats, formerly profuse diarrhea, tremor, formerly marked emaciation and high-grade nervousness; lately condition better, for years a stationary condition.

The protrusion of the eye balls is explained by most authors by an increased fullness of the orbital vessels. The rapid variations in the intensity that the protrusion of the eye ball shows in many patients have led to this assumption. The essential cause is however an abnormal tonus of the *Landström* muscular palpebralis, which is innervated by the sympathetic. The protrusion may be produced experimentally by electric stimulation of the cervical sympathetic (*Claude Bernard*). The protrusion may be such a high grade as to come to displacement of the globe. In old Basedow's cases it remains stationary, which may be explained through increased deposition of retrobulbar fatty tissue. On the contrary, the gaping of the palpebral fissure (*Dalrymple-Stellwag's* sign) on increased opening tension of the eye (*L. Bruns*) is dependent on an abnormal tonus of the oculomotor nerve, and is, therefore, according to *Eppinger* and *Hess* to be regarded as a sign of autonomous irritation.

The exophthalmus may also be unilateral. A confusion with unilateral affection of the sympathetic may be avoided by attention to the width of the pupils; the latter should show no differences in Basedow's disease; *Roasenda* has described three Basedow's cases with unilateral eye symptoms, and in one of these cases this symptom always remained limited to the one side. The unilateral exophthalmus sometimes accompanies unilateral enlargement of the thyroid gland, either with homolateral or with contralateral enlargement. *Worms* and *Hamant* have issued a compilation of such cases.

*v. Gräfe's* symptoms, *i.e.*, the failure of the upper lid to follow, or only retarded following of the upper lid when the vision is turned slowly downward, the white sclera thus becoming visible at the upper border of the cornea, depends on an increased tonus of the levator palpebræ muscle. *v. Stellwag's* symptom consists in a rarity and an incompleteness of the involuntary blinking. Whereas in the normal individual the blinking movement occurs three to five times in the minute, in Basedow's disease it may not occur for minutes.

The eye symptoms are very hard to reproduce experimentally a fact that for a long time stood in the way of the hypothesis that Basedow's disease was a hyperthyrosis; however, *Kraus* and *Friedental* and *Hönicke* were finally successful, through the administration of very large amounts of thyroidin in inducing a widening of the palpebral fissures and an exophthalmus, although not to a very marked degree. Recently through the use of material obtained by the removal of struma at operation on human beings it was possible to induce typical exophthalmus in a dog (*Lampé*, *Lesegang*, *Klose* and *Baruch*.) Worthy of mention here is also the case of *Nothafft*, in which an evident protrusion developed after an excessive use of thyroid gland tablets.

Finally, *Möbius's* symptom consists in a weakness of convergence; by fixation of the finger held near-by, the eye deviates without diplopia; perhaps this not common symptom is to be explained by a fatty degeneration of the eye-muscles, that is observed in severe cases of Basedow's disease. Also pareses and paralyses of the eye-muscles have been observed. *Kappis* describes a case in which the beginning of the illness occurred eleven years previously; with gradual increase in all symptoms there developed an extensive paralysis of the eye-muscles and other cranial nerves. *Kappis* has collected forty cases of eye-muscle paralysis in morbus Basedowi.

Sometimes there occurs in Basedow's disease an excess of tears (*Berger*); sometimes, however, an abnormal dryness of the eye. In high-grade protrusion the cornea may ulcerate and erode, the lens may fall out, and the panophthalmia that develops may lead to death. Patients with Basedow's disease bear cataract operation badly (*Möbius*). In rare cases there is observed atrophy of the optic nerves (also obtained experimentally through administration of thyroid gland, *Birch-Hirschfeld* and *Nonmbuo Ynvuye*); finally mydriasis sometimes occurs on instillation of adrenalin (*O. Löwi*). The adrenalin mydriasis is also found in experimental hyperthyroidism (*Eppinger, Falta*, and *Rudinger*).

The eye symptoms belong to the classic form of the disease. In the formes frustes they may be absent or only suggested. In the following briefly sketched case they were wanting altogether:

*Observation III.*—S. Schm, fifty-six years, shoemaker. For about thirty years diffuse enlargement of the thyroid, circumference of the neck 42 cm. Until six months ago, perfectly healthy. Then occurred gradual increase in the size of the neck to 43 cm. and then to 44 cm. Lassitude, sweatings, difficulty in breathing. His physician ordered for him an iodine cure that rapidly made matters worse. Severe dyspnea, cardiac palpitations, marked tremor, profuse sweats, and profuse watery diarrheas, the bowels moving ten to twelve times daily, loss of weight about 18 kg.

Markedly emaciated, skin moist, eye symptoms not present. Both lobes of the thyroid very much enlarged, the left somewhat larger, pulsation, vascular murmurs weak. Perithyroidal lymph-glands palpable. Cardiac shadows widened to 13 cm. as seen on X-ray examination, shadow of the aorta increased to 6 cm. tachycardia (110–130), leucocytes 8500, of which only 33.3 per cent. are neutrophiles. Slight tremor, sweats (Fig. 8).

Of the alterations in the **respiratory organs** are to mention first soundlessness of the voice (*Trousseau*), sensation of scratching in the throat, and tormenting, irritating cough (*Nothafft*). The irritating cough was first described by *Pierre Marie;* he found it in twelve of fifteen cases. This symptom may be very tormenting and may start in as an early symptom. It is accompanied by little or no expectoration. *Murray*, however, observed some cases in which there existed, a profuse expectoration, a veritable bronchorrhea which he brings into analogy with the profuse watery diarrheas of the patients (paroxysmal condition of excitement of the autonomous nerves). Further is to be mentioned the increase in the frequency of respiration, the superficial breathing and the air hunger, symptoms that occur paroxysmally even as early symptoms, but that often last for a long time. These symptoms are closely allied with the increased need for oxygen, that is, with the need for rapid loss of heat on account of the increased heat production. *Bryson's* sign—the patients are not able to expand the chest in the normal manner on deep inspiration of the thorax—has nothing to do with this, but depends apparently on a weakened condition of the respiratory muscles as a result of the fatty degeneration that was found by *Askanazy* in all the bodily musculature. The acceleration and becoming shallower of the respiration was also produced experimentally by *Fenyvessy* by the feeding of the thyroid gland substance to dogs. It was absent after cutting of the vagus nerves. The graphic registration of this breathing very clearly in Basedow's disease shows the shallowing of the respiratory efforts and the periodic cessation of respiration (increased tonus of the vagus, *Hofbauer*). *Eppinger* and *Hess* have observed these respiratory curves, especially in those Basedow patients who showed signs of increased tonus in other autonomous nerves.

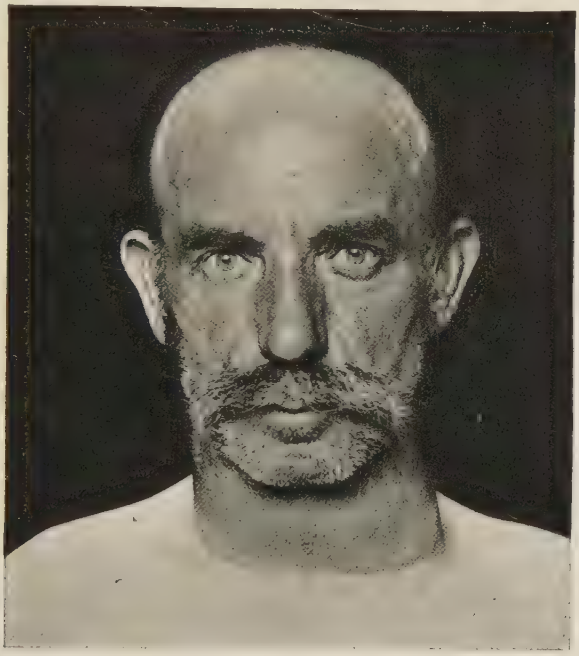

FIG. 8.—Absence of the eye symptoms in Basedow's disease.

To the **nervous symptoms** belong almost all the symptoms of Basedow's, as they are for the most part the expression of the condition of irritation of the vegetative nervous system. Of the nervous symptoms in the narrower sense is especially to be mentioned the tremor of the separated fingers, which was first observed in 1862 by *Charcot* and was later described by *Marie* in a monograph as the principal and initial symptom of Basedow's disease. *Nothnagel* has especially pointed out that the tremor is very fine. The observations of *A. Kocher* give an idea as to the frequency [of occurrence] of the tremor. *Kocher* found it clearly manifested in sixty cases out of sixty-three. Slight psychic emotions can make the tremor more evident. Intended movements do not ordinarily increase it. Fine coordinated movements may, however, be disturbed or make impossible on account of strong tremor. Very strong tremor may also assume a choreic character. In fully developed cases the patients are often in an "état de vibration perpétuelle." The tremor may also affect the tongue, eyelids, lips, the lower extremities, diaphragm, and respiratory muscles; the number of vibrations reaching about 8 to 9.5 in the second, as many as in progressive paralysis and alcoholism; while in senile tremor and paralysis agitans the number is less. The tremor may be readily reproduced experimentally by the feeding of thyroid gland.

An exactly similar tremor is seen sometimes transitorily in hysteria and neurasthenia, as the graphic registration has shown.

A further symptom is muscular weakness, even paraparesis of the legs has been observed (giving away of the legs). *Stern* regards this as hysterical. Also transitory monoplegias and hemiplegias have been observed. Not rarely occur drawing pains in the entire body, or only in the arms or legs, or in the shoulders, and especially in the neck. *Kocher* found them in a great number of his cases. *Möbius* does not believe that they are in direct connection with hyperthyrosis. This is, however, made certain by the investigations of *Falta*, *Newburgh*, and *Nobel*, who obtained the pains in numerous cases after the administration of thyroid gland substance. The same is also true of the headache, which is very common in Basedow's disease; indeed it may be the initial symptom and is very common in artificial thyroidism. Also the insomnia of the Basedow patient may occur as the initial symptom; in many cases it occurs for weeks, varying [in intensity], and may reduce the patient very much.

Almost always occur alterations in the **mental life,** abnormal irritability, unmotivated gaiety, hasty speech, rapid flow of thoughts, an indication of flight of ideas, rapid change of mood, terrifying dreams; the character alters, the patient becomes mistrustful, choleric, capricious, strikingly euphoric, or often very much depressed. *Möbius* happily compares this condition with a very slight "Rausch" in which a maniacal mood may readily occur, and in which a conversion into depression may readily follow. Attacks of laughing and crying may occur, and combination with hysteria is not rare. Sometimes the condition terminates in delirium, confusion with hallucination, and coma.

The transition of these mental alterations into a true psychosis is not rare. Often it is the maniacal conditions, often the depressions, that prevail. Also the picture of melancholia may develop. According to *Sattler*, out of one hundred and fifty cases in literature, more than seventy belong to manic-depressive insanity. For the comprehension of these alterations in the psychic life the observation is important that in individual cases similar conditions may occur after the administration of thyroid-gland tablets. Conditions of excitement are not uncommon in thyroidism. Cases of thyroidin intoxication insanity have also been observed (*Boinet*, *Parhan* and *Marbe*). The authors last mentioned observed two cases, in whom after the ingestion of great amounts of tablets there set in complete confusion and hallucination. The manifestations disappeared with the withdrawal of the administration of thyroid. The following case (*Falta*, *Newburgh*, and *Nobel*) is instructive:

*Observation IV*.—Woman, aged fifty, who for a half year had suffered loss of weight, headaches, insomnia, associated with psychic depression and thoughts of suicide. There was present also glycosuria. The condition gradually ameliorated and after some weeks' stay at the clinic the patient felt very well. Then the patient took thyroid tablets for three days, upon which the psychic depression and thoughts of suicide recurred. On the withdrawal of the drug these disappeared.

Already *Brunet* mentioned that Basedow's disease is not associated with any special psychosis; when a true psychosis occurs in it, we may well assume that a psychopathic predisposition already existed and that the hyperthyrosis constituted the determining factor.

Of the symptoms affecting the **digestive tract** we shall mention first increased flow of saliva. This symptom often occurs paroxysmally, and even initially; more rarely there is a dryness of the mouth. When the flow of saliva is increased, there is an increased tonus of the nerves of the salivary glands; when the flow is diminished there is an increased tonus of the sympathetic nerves of the salivary glands (formation of a thickly flowing secretion or irritation of the sympathetic nerves of the salivary glands (*Eckhardt*); also the noticeably increased diuresis may exercise an influence here. Toward an increased vagus tonus points also for the most part slight degree of acidity of the gastric juice, that is observed in rare cases of Basedow's disease (*Eppinger* and *Hess*). Sometimes crises of hyperacidity are observed (*Marañon*). Ordinarily, however, subacidity is present (*Wolpe*). Especially imporant symptoms are vomiting and diarrhea (*Pierre Marie*) because they greatly reduce the patient. Vomiting is found, according to *Sattler*, in 15 per cent. of all cases. Ordinarily it occurs paroxysmally, for the most part without any relation to ingestion of food, often without any nausea. When no food has been ingested it is usually thin; the paroxysm may last for a whole day, in which case the vomiting may occur thirty times during the day and be uncontrollable. For the most part it is unaffected by medication; it may disappear as rapidly as it came, and may be followed by a period of increased ingestion of food. More common are the profuse watery diarrheas (according to *Sattler* in 30 per cent. of all cases). For the most part they are painless—twenty to thirty stools a day may occur. They may lead to scaphoidal retraction of the abdomen as in cholera (*Fr. v.*

*Müller*). The diarrheas also are hardly to be affected by medication. In rarer cases, admixture with blood may be observed. Vomiting and diarrhea may also be produced in animal experimentation by feeding with or injection of thyroid gland substance. In human beings, sometimes only shortly continued administration of thyroid gland tablets may suffice to produce action on the bowels. In two cases, *Falta*, *Newburgh*, and *Nobel* observed that on the third day of the thyroid medication the previous solid stools, that occurred only once a day, had now become soft and failed to show the impressions of the haustra, and that on the third day two soft stools occurred. On withdrawal of the medication, the stools again showed their former consistency. *Kocher* observed one case with obstinate constipation, in which simultaneously with the appearances of the rather acute development of Basedow's, diarrheas developed. The statement of *Kocher* that in none of the sixty-three cases of Basedow's described by him did constipation exist, dare not be generalized. I have seen several cases of formes frustes with constipation (see Observation V). *Möbius* regards the profuse diarrhea of morbus Basedowi as the expression of the effort to cast out the thyroid gland substance that is circulating in excess. From this standpoint it would not be uninteresting to test the stools as to their iodine contents. It is safe indeed to assume a marked increase in the secretion in the intestines. This and the paroxysmal occurrence confirms the assumption of *Möbius*. In the higher degrees, there is, in addition, apparently slight inflammatory swelling of the intestinal mucous membrane; at least we may observe this in experiments on animals; where in the highest degrees of thyroidism hemorrhages into the mucous membrane may occur. Also an increased secretion of the pancreatic juice may, in accord with the experiments of *Balint* and *Molnár* be assumed; these authors found in the watery evacuations an abnormal quantity of tryptic and diastatic ferment. Whether we may see in the profuse diarrheas an expression of vagotony, as *Eppinger* and *Hess* believe, appears to me questionable, as vagotony is inclined to go hand in hand with spastic obstipation.

We should sharply distinguish from these profuse diarrheas the *disturbances of fat absorption* that are sometimes found in morbus Basedowi. *Adolph Schmidt* and *H. Salomon* have just described one case apiece. I have added seven cases, in which, as in *Salomon's* case, the fat-splitting was relatively good, so that the disturbances lay especially in the absorption. In the case very carefully investigated by me the dry substance contained 53 per cent. fat, of which 24.7 per cent. was neutral fat, 44.2 per cent. soaps and 31.1 per cent. fatty acids. Sometimes the fat stools are found only on the overloading of the intestines with fat (*v. Noorden*). Of late *Bittorf* has contributed a pertinent case. I here report two others:

*Observation V.*—Ad. K, thirty-three years, locomotive stoker, entered the first medical clinic December, 1911. No hereditary taint, was always well until November, 1905.

Then struck by a locomotive, fell on the left side, for three weeks hematuria and fever. At the beginning also unconsciousness, then severe headache, vertigo, nausea. Immediately after the accident began tremors, palpitation, anxiety, insomnia, and twitchings in the lower extremities. Eight days after the accident, the patient noticed an enlargement of the right lobe of the thyroid gland. Soon afterward marked pulsating in the vessels of the neck and oppressive feeling of heat, and burning of the skin of the throat and neck. This condition continued from this time on without essential alteration. The patient states that he has become peevish and irritable and afraid of people. His muscular strength has diminished, he tires easily, and often has drawing pains, also headaches, vertigo, and sometimes vomiting, also very heavy sweats. Ordinarily slight constipation, from time to time a period in which three or four broth-like evacuations of a gray color occur daily.

Rather thin; the face especially, but also the skin of the throat and upper part of the breast a burning red. On disrobing and on excitement the redness increases. Pronounced dermographism. On stroking the skin with the handle of the percussion hammer there are elicited streaks the breadth of which is that of a finger.

The right lobe of the thyroid is enlarged, about the size of an apple. Surface smooth, elastic but not hard in consistence, evident pulsation, vascular murmurs. In the neighborhood, enlarged lymph-glands. Points of exit of the trigeminal nerves tender to pressure. Slight paralysis of the sympathetic on the right. All eye symptoms negative. To Röntgen examination slight widening of the shadow of the aorta to 6 cm., and of the heart to 12–½ cm. Pulse 120–140.

Blood pressure, according to *Riva-Rocci*, taken on the arm 140. On the left middle finger (*Gärtner*) 85.

Later measurements:
*Riva-Rocci*, 130–120;
*Gärtner*, 70.
After two weeks:
*Riva-Rocci*, 120–110;
*Gärtner*, 55.
Blood: Erythrocytes, 5,000,000.
Leucocytes 9200, of which:
Polynuclear neutrophiles, 53 per cent.
Lymphocytes, 32 per cent.
Large mononuclears, 14 per cent.
Eosinophiles, 1 per cent.

Several later blood examinations gave similar results.

Alimentary glycosuria (100 gm. dextrose) 4.24 gm. of sugar.

The stools frequently show the luster of fat and a gray color. After 250 gm. of oatmeal and 300 gm. butter, typical fat stools. The microscopical examination shows little neutral fat, but many soap balls and fat needles.

Profuse sweats, in which the bedclothes are soaked through. On the soles of the feet exist pea- to bean-sized vesicles filled with serous fluid, which burst so that the cutis lies exposed.

Marked tremor of the hands, intensified on movements.

Examination of the fundamental exchange (*Dr. Bernstein*).

| $CO_2$ | $O_2$ | RQ | Per kilogram body weight | |
|---|---|---|---|---|
| | | | $CO_2$ | $O_2$ |
| 237.6 | 289.0 | 0.804 | 3.25 | 4.17 |
| 220.2 | 293.0 | 0.741 | | |
| 230.1 | 296.5 | 0.776 | | |

The fundamental exchange is therefore somewhat increased.

Result: Forme fruste of Basedow's after trauma with all important symptoms (tachycardia, sweats, tremor, increase of the fundamental exchange, mononucleosis) with exception of the eye symptoms. In addition, fat stools and alimentary glycosuria.

*Observation VI.*—A. Schr., woman aged thirty-three years. First entered clinic Jan. 9, 1913. Father was very nervous and easily excited. Menstruation, which began at the age of fourteen years, occurs regularly every four weeks, lasts four to eight days, not painful. Seven years ago, luetic infection, after which unilateral headache, for one year diplopia. Two children, that are very nervous, two miscarriages, the one before the infection, the other after it. For three months menstruation very sparse.

The present illness began three months ago. At first insomnia and severe headaches, then marked palpitations. Dyspnea, profuse sweats, severe tremors in the hands and feet. Conditions of excitement, sometimes vomiting. During the last three months has lost about 10 kg., the throat is enlarged, for six weeks the eyes protrude. During the first week five to six stools daily, of normal consistence, but of a *white-grayish* color.

Exophthalmus distinct, but not marked. Thyroid enlarged, diffusely, distinct tremor, marked tachycardia.

Blood-pressure. Gärtner, 95. Riva-Rocci, 135.

Leucocytes 5500 (of which 55 per cent. polymorphonuclear neutrophiles and 1 per cent. eosinophiles).

Alimentary glycosuria positive (with 100 gm. dextrose 0.57 gm., with 50 gm. dextrose 2.4 per cent. with 30 gm. dextrose, negative).

Overloading with fat at present does not lead to fat stools. No diarrhea now.

The cases with fat stools all seem to show certain characteristics. Almost always they are formes frustes with absent or slightly developed eye symptoms. In addition all cases up to the present have shown latent disturbances in the carbohydrate metabolism. In three cases, the disease developed after a trauma. For a close relationship between thyrogenic glycosuria and fat stools speaks also the observation that both disturbances retrogress simultaneously either spontaneously or after therapeutic procedures (exposure to Röntgen rays). It is not unlikely that both come about through an inhibition of the internal secretory activity of the pancreas. At least there must also be assumed a direct action of the excessively produced thyroid gland secretion on the intestinal mucous membrane, for indeed in diabetes mellitus the absorption capacity of fat is perfectly normal. I do not speak here of the fat stools in cases of diabetes mellitus with closure of the pancreatic ducts, as in these it is known that the disturbance in the splitting of neutral fat is prominent. The observations of *Balint* and *Molnár*, that I have already mentioned, do not speak, as these authors believe, against my assumption, as they are dealing with watery diarrheas that have nothing to do with fat stools and that mostly occur in the other forms of Basedow's disease. Up to the present I have seen only one case with fat stools in which formerly profuse diarrheas had existed.

The examination of the **blood** in Basedow's disease usually gives normal figures for the red blood cells and the hemoglobin. In cases where a diminution is present, the iron-content is, according to the investigations of

*Rossin* and *Jellinek*, very much reduced. The coagulation capacity of the blood is in the most cases delayed. *Kottmann* and *A. Lidsky* found in thirty-seven cases this delay in 78.3 per cent., a normal coagulation time in 5.4 per cent., and an acceleration in 16.2 per cent. In the cases in which it was delayed, it approximated normal figures after operation. The delay also exists in experimental hyperthyroidism (*Kostlivy*). These facts explain why in operations on Basedow's patient the control of hemorrhage is often difficult. According to *Kottmann* the serum of Basedow's patients works in a retarding way on autolysis; also the freezing-point lies lower than under normal conditions. *Fr. Kraus* and *Friedenthal* found that the blood-serum of Basedow's patients acts in a mydriatic manner. *A. Fränkel* found an increased action on the wave-motions of the rabbit-uterus after the death of the animal. These findings do not point absolutely to an existing adrenalinemia (*O'Connor, Falta, Fleming*). Therefore the far reachings, conclusions that *Kostlivý* has drawn from these findings, as to the sympatheticotonizing components of the secretion of the thyroid gland are purely hypothetical. Of greater importance is the alteration in the leucocyte formula first described by *Th. Kocher*. There exists at first a slight leucopenia and almost regularly also in the early stages mononucleosis. The statements of *Kocher* have been confirmed by numerous investigations (*Caro, Ciuffini, Gordon* and *v. Jagič, Roth, Bühler, Kappis, van Lier, Kostlivý, Turin* and *others*). The mononucleosis is also found in the formes frustes; but it is also common in struma without Basedow's symptoms (*Müller, Ch. Kappis, von Lier,* and *others*). Cases of Basedow's with absent mononucleosis seems to belong to the great exceptions (*Kostlivý, Roth, Borchardt, the author*).

*Observation VII.*—C. A., twenty-one years old, student. For about six weeks rapid enlargement of the thyroid gland. Former circumference of the throat 39 cm., now 42 cm. Tachycardia, labile pulse, sweats, tremor, stools formerly sluggish, also sluggish at present. Diffuse enlargement of the thyroid gland, consistence weak, pulsation of the carotid. No eye symptoms. Apex-beat broadened and increased. In the urine traces of sugar, after overloading (2 rolls, four pieces of sugar), 2 per cent.

Blood examination:
Leucocytes, 7000 of which:
Neutrophiles, 68.6 per cent.
Lymphocytes, 25.3 per cent.
Mononuclears, 4.6 per cent.
Eosinophiles, 1.5 per cent.

After several months, essential improvement in all manifestations, high tolerance for carbohydrates.

It seems to me, however, that great caution is necessary in regarding the blood picture in cases of Basedow's as normal, as the alterations of the blood picture, like those of the other symptoms of Basedow's undergo great changes. The following is a case in point:

*Observation VIII.*—Fl. R., woman, thirty-five years of age. First came under observation Dec. 12, 1912. Apparently no hereditary nervous predisposition. Menses first appeared in the eleventh year of life, flow abundant, regular, lasts for three days every four weeks. Five normal births. Three years ago a miscarriage at the second month. Since this time development of Basedow's disease. Since that time menses are accompanied with severe pain, especially backache. The flow is less in amount. When the exophthalmus first developed, her face took on a terrified appearance, which her acquaintances observed; she felt very well otherwise, and the ophthalmologist made the diagnosis, Basedow's disease. Only several months afterward began to develop watery diarrheas, cardiac palpitations, dyspnea, nose-bleeds, headaches, rheumatoid pains in the extremities, lassitude, sensation of dizziness, and extraordinary psychic irritability; the condition gradually became worse, with a transitory period of amelioration during the summer before I saw her. There occurred moreover insomnia, sweats, pains in the calves, pain in the forehead and eyes on reading, also transitory marked flow of ears. The appetite very changeable, at times voracious appetite, then again anorexia.

Distinct protrusion, *v. Gräfe's* symptoms plainly positive, *Löwi's* symptom plainly positive. Tachycardia extremely variable, the pulse varying from 80 to 150. Subjectively, rather marked oppressions; marked falling-out of hair, inclination to slight rises of temperature. Marked sweats, very variable. Thyroid gland diffusely enlarged (right lobe somewhat more than the left) soft, plainly pulsating, distinct palpable thrill, over it a diastolic vascular murmur.

Alimentary glycosuria (200 gm. dextrose) negative.

Blood-pressure—*Riva Rocci* 130, *Gärtner* 85; these differences were regularly found on repeated examinations.

At the beginning of the observation the above symptoms were present, only the tachycardia is very slight and the tremor of the hands scarcely demonstrable.

The blood examination now shows:

Leucocytes, 8000 of which:

Polymorphonuclear neurophiles, 70 per cent.

Eosinophiles, 2 per cent.

Lymphocytes, 21 per cent.

Large mononuclears, 7 per cent.

Later the condition became worse, the pulse rate rose to about 130, the tremor became distinct, the blood examination now gave 9000 leucocytes, of which:

Polymorphonuclear neutrophiles, 60 per cent.

Eosinophiles, 2 per cent.

Lymphocytes, 27 per cent.

Large mononuclears, 11 per cent.

Also the examination of the respiratory exchange of gases gave indeed always an essential increase, but appreciable variations (*Dr. Bernstein*)

| | $CO_2$ | $O_2$ | $CO_2$ per kg. and m. | $O_2$ per kg. and m. | RQ |
|---|---|---|---|---|---|
| On Jan. 12th | 220.5 | 280.5 | 3.82 | 4.86 | 0.786 |
| 15th | 213.1 | 270.8 | 3.67 | 4.67 | 0.787 |
| 16th | 229.9 | 316.9 | 3.96 | 5.46 | 0.725 |
| 19th | 238.6 | 284.5 | 4.11 | 4.90 | 0.839 |

Also the examination of the excretion of urine showed in the first period 0.45 and 0.37 gm. U. (on the 7th and 8th day of the purin free diet).

In the second period 0.52—3rd day of the purin free diet.
0.78 20 gm. sodium nucleinate (the greater part vomited).
0.53
0.75 200 gm. meat.
0.61

In this case we find therefore, in spite of very evident Basedow's symptoms the blood picture at first normal, and then only later did it show the typical changes in the blood. I observed a short time ago a still more striking case. Here in the beginning all the typical signs of a Basedow's disease were present. The tremor was especially strong. The blood examination showed 8800 leucocytes with 65.8 per cent. polymorphonuclear neutrophiles, 2.2 per cent. eosinophiles, 0.5 per cent. mast-cells, 5.5 per cent. transitionals and 26 per cent. lymphocytes. After two weeks another blood examination was made. This showed 53 per cent. polymorphonuclear neutrophiles, 7 per cent. eosinophiles, 0.5 per cent. mast cells, 45.5 per cent. lymphocytes. The clinical picture was not essentially changed otherwise. It is worthy of mention that for some days before the second count much meat had been ingested.

For the judgment of the blood alterations in Basedow's disease it is important to note that the mononucleosis increases on the ingestion of thyroid gland tablets, while, as we shall see later, the mononucleosis decreases in conditions of athyrosis, and the blood picture approaches the normal. This relationship was first described by *Falta*, *Newburgh*, and *Nobel;* and lately *Th. Kocher*, apparently without knowing our work, has written about the practical significance of this finding.

Intercurrent febrile diseases bring about the transitory disappearance of the mononucleosis (*Roth*) I have seen a case of Basedow's disease, in which a croupous pneumonia developed. Before this occurred, there were 6200 leucocytes with 46 per cent. neutrophilic cells, at the height of the pneumonia were 17,100 leucocytes with 87 per cent. neutrophiles. Also shortly after the removal of the struma in patients with Basedow's occurs, as is known, a transitory neutrophilic hyperleucocytosis.

The mononucleosis is readily produced experimentally by feeding with thyroid-gland tablets. *Bertelli*, *Schweeger*, and *I* have regarded it as the expression of an excitation of the autonomous system. *Eppinger* and *Hess* have explained in like manner the hypereosinophilia sometimes observed in Basedow's disease. We must consider in this connection not only the absolute or often only relative increase in the mononuclear cells, but must regard as of value the relative and always absolute diminution in the neutrophilic cells in the peripheral vessels. In the cases with leucopenia the number of mononuclear cells is not increased absolutely, in spite of the marked relative increase; here the alteration of the leucocyte formula is brought about exclusively through the marked deficiency in neutrophilic cells. In the initial stage, especially on sudden overdissemination of thyroid glandular secretion there may well be chiefly an abnormal distribution of the neutrophiles in the vascular tree, leading to the above-mentioned leucocytic formula; as after feeding with thyroid substance to dogs we found in the capillary blood of the livers of these dogs hyperleucocytosis with marked pre-

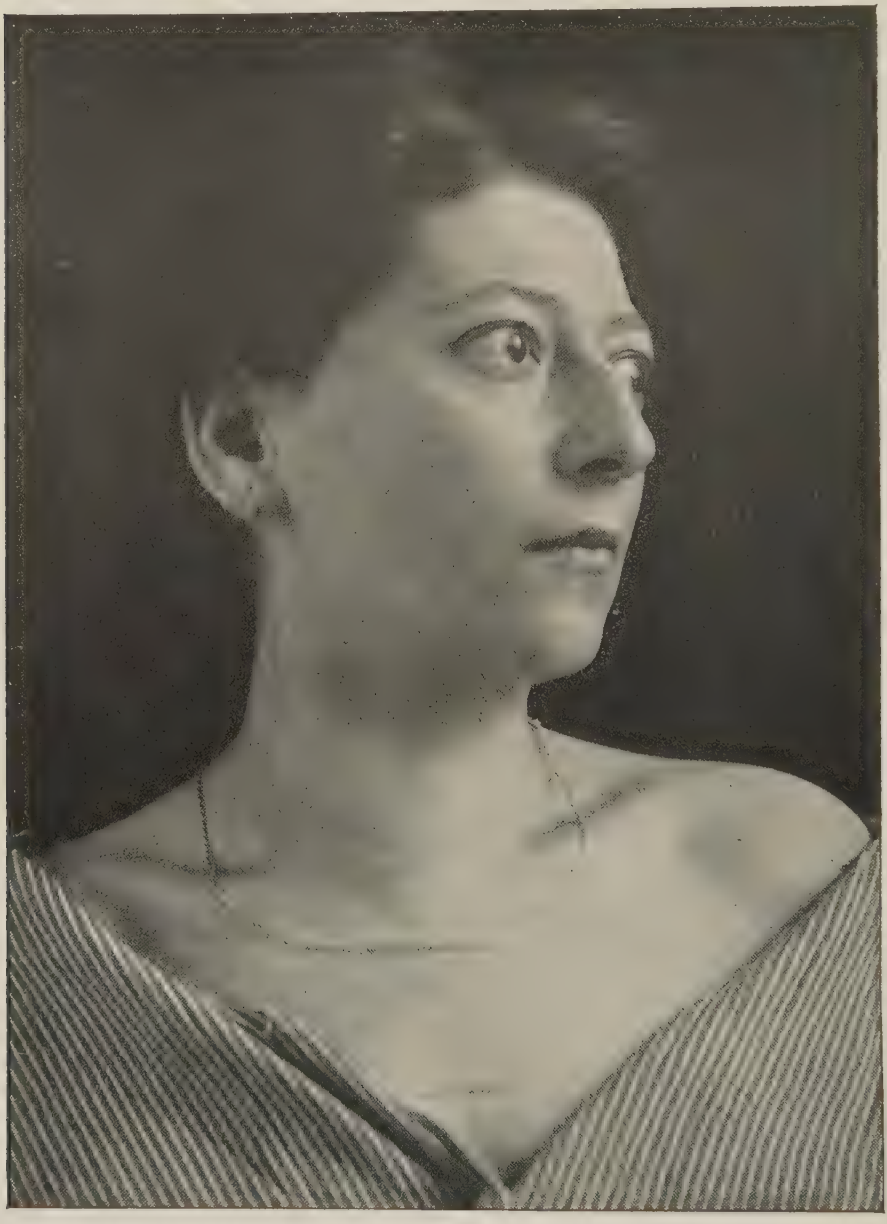

FIG. 9.—Diffuse enlargement of the thyroid gland in Basedow's disease.

dominance of the neutrophilic cells. Later there comes about a permanent alteration of the hematopoietic apparatus, consisting in a hyperplasia of the lymphatic apparatus. With this alteration stand in harmony the swelling of the lymph-glands so often observed in Basedow's disease (*Gowers*), especially the swelling of the perithyroidal lymph-glands (*Fr. Müller*, *Passler*, *Kocher*, and *others*), and also the perivascular round-cell infiltration of the typical Basedow struma, the hyperplasia of the rest of the lymphatic apparatus (*Fr. Müller* and *others*), the tonsils, lingual papillæ, intestinal follicles, the hyperplasia of the spleen and the thymus gland (*Bonnet*, *Gierke*, *Thorbecke*, *v. Hansemann*, *Rössle*, *Hart*). In severe acute cases, a distinct splenic tumor can appear as an early symptom. *Schlesinger*, a short time ago, reported such a case. Of late great practical significance has been ascribed to the hyperplasia of the thymus. According to *Capelle's* statistics, 44 per cent. of the cases of Basedow's disease that died of intercurrent diseases showed a hyperplasia of the thymus, 82 per cent. of the cases that died of Basedow's disease itself, and almost 100 per cent. of the Basedow's cases that died on operation. In these cases it is questionable whether the thymus hyperplasia is responsible for the death. Perhaps death was due more to the status lymphaticus, perhaps more to the failure of the chromaffin organs. I shall defer the consideration of the thymogenic Basedow's disease until the discussion of the theory.

Of the **metabolic disturbances** should be mentioned first of all the emaciation, which is so important practically. *A. Kocher* found this, for example, in 88 per cent. of the cases among his very large number. It is present in the fully developed form. It may set in very early and progress in a uniform manner; in other cases it may increase in acute exacerbations that may frequently be repeated (crises d' amaigrissement, *Huchard*). Almost regularly such periods of increased emaciation are associated with the increase of other Basedow's symptoms. In the fully developed forms 15–20 kilograms may be lost in a few months. Also in the incomplete forms, a slight grade of emaciation is absent, relatively seldom. In the cases of Basedow's in which the emaciation is marked, there not infrequently develops a severe grade of cachexia (cachexie thyreoidienne, *Gauthier*). In other patients there may gradually set in a reversal of affairs, in which the loss may be more or less rapidly made up. In rare cases, even obesity may develop. In the great majority of cases the appetite is increased, especially at the beginning; and there is often polyphagia. Of course the increase of appetite often remains behind the much greater requirements. Later the appetite often becomes less. If vomiting or diarrheas are superadded, the body weight rapidly falls.

The cause of emaciation in spite of the increased appetite depends in part on an increase of the caloric production through the thyroid secretion produced in excess. *Fr. v. Müller* first pointed out that in spite of the abundant supply of calories, in Basedow's disease the body weight often falls. The demonstration, that the *fundamental exchange*, that is the $CO_2$ production and the $O_2$ consumption in a fasting condition with the exclusion of all muscular activity, is in Basedow's disease increased, was first furnished by *Magnus-Levy*, and later by *Thiele* and *Nehring*, *Stüve*, *H. Salomon* and *others*, by means of the *Zuntz* apparatus. *Steyrer* investigated the increase of exchange by the *Voit-Pettenkofer* respiration apparatus. In the severer cases the increase of exchange may reach 70 per cent. I reproduce here *Magnus-Levy's* instructive table:

| | Age, years | Height cm. | Weight, kg. | $O_2$ cc. | $CO_2$ cc. | $O_2$ cc. per kg. | Per cent. normal values |
|---|---|---|---|---|---|---|---|
| 1. Acute, very severe case.......... | 20 | 158 | 50.7 | 348.9 | 295.0 | 6.89 | 170 |
| 2. Very severe chronic case......... | 26 | 150 | 50.5 | 344.0 | 236.2 | 6.80 | 170 |
| 3. Severe chronic case............. | 22 | 161 | 55.1 | 305.8 | 256.0 | 5.55 | 142 |
| 4. Somewhat higher chronic case... | 55 | 156 | 43.9 | 266.9 | 299.3 | 5.31 | 122 |
| 5. Light case..................... | 20 | 148 | 55.0 | 213.2 | 181.1 | 4.74 | 105 |
| 6. Cured by operation ten years ago | about 40 | 171 | 84.0 | 282.8 | 241.0 | 3.37 | 100 |
| 7. Simple goiter.................. | 66 | 142 | 50.5 | 176.7 | 143.1 | 3.43 | 90 |

A very interesting example is furnished by the following case investigated by *Dr. Bernstein.*

*Observation IX.*—H. J., twenty-two years old, pronounced true infantilism. Two years ago and one year ago tetany, simultaneously with aggravation of a stomach affection that had lasted a long time. With the decline of the second period of tetany pronounced manifestations of hyperthyrosis. After a gastroenterostomy there was no recurrence of the tetany. The Basedow's manifestations (tachycardia, sweats, tremors) remained, or improved only a little. Eye symptoms were entirely absent. The investigations of the fundamental exchange gave

| $CO_2$ | $O_2$ | RQ | Per kilogram of body weight | |
|---|---|---|---|---|
| | | | $CO_2$ | $O_2$ |
| 182.2 | 229.1 | 0.796 | 4.45 | 5.61 |
| 180.2 | 227.4 | 0.793 | | |
| 185.6 | 222.1 | 0.836 | | |

In other cases *Salomon* could show that the caloric production is also present in the formes frustes. The case just detailed (Observation IX) and Observation V agree in that they show that the increase of the exchange may also be distinct in the formes frustes that pursue their course without eye symptoms.

Further I would refer to Observation VIII where the examination of the gaseous exchange showed that like the rest of the Basedow's symptoms the caloric production is subject to great variation.

The increase of fundamental exchange may also be demonstrated experimentally through the administration of thyroid gland; it is, however, not very great, and in some individuals remains absent.

The question as to which way the increasing influence of the thyroid gland secretion acts on the metabolism has been much discussed. The tremor alone is not responsible for it, as after exclusion of the tremor by hyoscine the exchange is not essentially reduced (*Magnus-Levy*). This author believes in a raising of the exchange in the resting cells. *Andersson* and *Bergman* have contradicted this, as after large doses of iodothyrin and thyroidin they found no increase on complete relaxation of the muscles and in sleep. These experiments however do not show very much, because, as previously mentioned, many normal individuals behave refractorily to the administration of thyroid gland. To my mind, we should not leave unconsidered in the explanation of the increase of the fundamental exchange the violent increase of tonus of the whole vegetative nervous system and the heightened activity of the organs affected by it. The increase of the caloric production cannot alone constitute the cause of the emaciation, but there must be added to it a disturbance in the regulatory mechanism that governs the taking up of nutrition. Here comes into consideration especially the disturbances of the stomach and intestines. I refer to what I have said on this subject in the first chapter.

In Basedow's disease is also the *albumin exchange* increased, that is, the individuals affected need more albumin or more oxygen-free energy especially in the form of albumin-sparing carbohydrates to maintain themselves in nitrogen equilibrium. In the accounting of the equilibrium must be considered also the N-loss on account of profuse sweats. *Hirschlaff* estimates it as 2–4 gm. in twenty-four hours. As is the case with all the other Basedow's symptoms, the increase of the albumin exchange may show great variations.

The increase of the albumin exchange is shown very prettily in the experiments of *Rudinger*. In a nearly N-free diet, rich in carbohydrates and fats (according to *Landergreen*), in normal human beings, the nitrogen in the urine falls rapidly to 4–5 gm. a day. In Basedow's patients, *Rudinger* found 7–8 gm. N. on the fourth day. The increase of the albumin exchange may also be demonstrated experimentally by the feeding with thyroid gland substance. *Bleibtreu* and *Wendelstadt* saw after administration of thyroid gland tablets in human beings a negative N-equilibrium that could be raised by by the addition of butter and sugar. Since the time of *Bleibtreu* and *Wendelstadt's* experiments, many investigations have been carried out that show the raise in the albumin exchange through thyroid medication (*Mayerle*). In a experiment of *Matthes* there was shown after strumectomy, with the patient on the same diet, an improvement of a previously negative N-equilibrium. On the administration of dried goiter, the excretion of nitrogen rose again. Also in animal experimentation could be demonstrated a rise of the albumin exchange (*Fritz Voit*). This was shown plainest in investigation of the metabolism on fasting (*Eppinger*, *Falta*, and *Rudinger*).

The question whether in hyperthyroidism the increase of the albumin exchange is primary or only the result of an increased carbohydrate and fat exchange is mostly answered that the increase of the albumin of exchange is primary. *Fritz Voit* found in dogs after feeding with thyroid gland substance a negative nitrogen equilibrium even when the diet contained abundant fat, so that fat could even be deposited [in the body]. This experiment does not seem conclusive as the nitrogen-free energy in the diet was exclusively upheld by fat. The same objection may however be made against the statement of *Magnus-Levy* that on the administration of fat or on abundant fat deposition, the loss of nitrogen is indeed appreciably restricted, but not entirely done away with altogether. In the mentioned experiment of *Rudinger* the elimination of nitrogen could be depressed to the *Landergreen's* minimal quantity, if larger quantities of nitrogen-free energy (with abundant carbohydrates) were ingested for a long time. We can therefore draw the conclusion that in hyperthyroidism there exists only a heightening of the physiological relations. This is indeed true for the lighter grades, but in the higher grades the degenerative changes of the muscular substances such as are described by *Askanzy*, speak for a toxic disturbance.

*Jaquet* and *Svenson* state that in the Basedow's patients the exchange after ingestion of food is raised higher than in normal individuals. In the investigations of *Porges* and *Pribram* the fundamental exchange after transitory copious administration of albumin was found to be abnormally high. It therefore seems as though the metabolism of Basedow's patients were especially labile, the administration of albumin perhaps increasing the activity of the thyroid gland in an especial manner. For this perhaps speaks also the fact that we can make the thyroid of dogs extremely poor in iodine by abundant administration of meat, this pointing to a rapidly leading off of the specific secretion; also, as is known, the Basedow struma is characterized by its very slight iodine contents.

The disturbances of *carbohydrate metabolism* in Basedow's disease do not seem to be of a uniform nature. There exists a combination of hyperthyroidism with true diabetes (*v. Noorden*, *Ewald*, *Grawitz*, *Hannemann*, *Bettmann*, *Falta*, and *others*). This diabetes shows only a slight dependence on the course of the hyperthyroidism. In the cases I described, X-ray irradiation had only a slight influence on the elimination of the sugar. With this agrees the fact that in true diabetes mellitus we can influence the sugar elimination by administration of thyroid gland only in the aglycosuric condition or on light glycosuria, while in the higher grades of glycosuria the influence is not so prominent. Also in the dog after complete extirpation of the pancreas under the administration of thyroid gland tablets there was no appreciable increase of the D : N quotient. In my cases of diabetes and Basedow's there were profuse diarrheas, while cases of true thyrogenic glycosuria of which I shall speak presently, show disturbances of fat absorption on overloading with fat.

The combination of Basedow's with true diabetes is not so rare. *Sattler* has collected forty cases from the literature. In twenty-six cases the Basedow's disease was present before the diabetes, in eight cases the diseases appeared about the same time, in the rest the Basedow's occurred in the course of the diabetes.

In many individuals the hyperthyroidism determines a predisposition for glycosuria. The disturbance may be occult, that is, glycosuria appears only on the administration of large amounts of pure grape-sugar. The alimentary glycosuria in Basedow's disease was first described by *Kraus* and *Ludwig*, and by *Chvostek*. It seems to have its complete experimental correlate in the alimentary glycosuria which may be elicited on the abundant administration of thyroid gland tablets in many normal individuals and in animal experiment (*Ewald*, *J. Dale*, *Dennig*, *v. Noorden*, *Bettmann*, *Georgjewsky*, *Strauss*, and *others*). The disturbance in the carbohydrate metabolism may, however, also be manifest, that is glycosuria is found on mixed diet. Such cases of spontaneous glycosuria do not appear to be common (*Lewin*, *v. Nothafft*, *A. Kocher*, *Falta*). Also Observation VII, reported previously, belongs to this group. *The glycosuria is characterized as thyrogenic by the fact that it comes on with the development of Basedow's disease, and disappears again with its ameloriation, and that after the cure of the Basedow's also the overloading tests show entirely normal relations.* It is to be distinguished from the alimentary glycosuria of Basedow's in degree only, as the alimentary glycosurias also disappear on the spontaneous or therapeutically induced improvement of the Basedow's. This is observed specially after X-ray irradiation of the thyroid (*Schwarz*, *Hirschl*, *Falta*). The thyrogenic glycosuria seems chiefly to occur in traumatic Basedow's, and, as had been mentioned previously, is frequently combined with disturbances of fat absorption.

In the *combination of Basedow's with true diabetes* there may well be assumed, in addition to the disease of the thyroid gland, an independent lesion of the insular apparatus of the pancreas. On the other hand I would regard that in the true thyrogenic glycosuria the hyperthyroidism brings with it a marked additional loading of the internal secretory activity of the pancreas, whether the thyroid glandular secretion inhibits the internal secretory activity of the pancreas, or whether the activity of the internal secretory activity of the pancreas is weakened somewhere else in the body. If, however, the pancreas is not equal to the necessary breadth of function, especially if an alimentary overloading is added, glycosuria makes its appearance. This hypothesis seems to be explained in an unforced manner: 1. by the fact that hyperthyroidism does not lead to glycosuria in all individuals; 2. that the glycosuria disappears with the retrogression of the hyperthyroidism, and that after this retrogression alimentary overloading does not lead to glycosuria. Distinction of the pancreatogenic from the thyrogenic glycosuria is not attended with any difficulty but there are, however, transitions, that is to say those cases in which the glycosuria occurs under the use of thyroidin medication (*Fried. Müller*). In such cases, just as in the case of *Ewald* (myxedema in which diabetes developed on the continued use of thyroidin medication and persisted after its withdrawal) might very well be supposed also a disease of the insular apparatus, that up to the time had been latent, and that had been made manifest through the thyroidin medication.

For the understanding of many of the characteristics of the metabolism in Basedow's patients we must note that the action of thyroidin depends on the constitution of the affected individual. As was mentioned previously, in normal individuals the action of thyroidin on the gas exchange, the albumin and the carbohydrate metabolism is often intensive, while other individuals are entirely refractory to the same dose of thyroidin. The constitutional differences probably lie in the different degrees of excitability of the vegetative nervous system, and this has perhaps its deeper foundation in the different reaction capability of the ductless glandular system. Now it seems that in Basedow's patients alterations of constitution occur in the course of the disease. So, for example, *v. Wagner* mentions a case of Basedow's disease, in which the initial rapid emaciation was followed by the development of an obesity, that had the characteristics of an essential obesity. Not so very rarely, too, are observed cases of Basedow's disease in which the initial rapid emaciation changes to a condition in which the patients not only recover what they have lost, but when placed on a little superfluous diet, they become fat in spite of the fact that they may still show symptoms of hyperthyroidism. *Magnus-Levy* reports a case of Basedow's that after subjective and objective amelioration received daily for four and one-half weeks two or three thyroidin tablets, without there occurring an aggravation of the Basedow's symptoms or an increase of the exchange of gases. A similar case was observed by the author. It was that of a forme fruste with distinct Basedow's symptoms (without eye symptoms) and glycosuria. After X-ray irradiation of the thyroid gland all symptoms disappeared; and high tolerance for carbohydrates soon came on. When the patient again presented himself after several months, thyroidin medication for three days (nine tablets a day) could be administered without an appearance of increase of the pulse rate or of alimentary glycosuria.

The thyroid gland secretion has an enormous influence on the *salt metabolism*. As *W. Scholz* first pointed out, it increases the elimination of phosphorus, especially through the intestine. The increase [of the phosphorus] in the feces may reach as much as 25 per cent. Older observations of *v. Noorden* and the later ones of *Oeri* have shown that the distribution of phosphorus to the kidney and intestine is exclusively dependent on the elimination of calcium; of calcium only a very slight part is to be found in the urine, by far the greater part is to be found in the feces. When the calcium elimination increases, a part of the phosphorus goes to the intestine with the calcium. Investigations of *Bolaffio*, *Tedesco* and the *author* on fasting dogs show that under the influence of thyroidin the $N:P_2O_5$ quotient in the urine is markedly increased, and that further, in agreement with *Scholz*, the elimination of phosphorus in the feces is very much increased and that the abnormal distribution of phosphorus to the kidneys and intestine is called forth by an increase of the calcium elimination by way of the intestine.

It should be mentioned further that in Basedow's disease *Forschbach* found strikingly slight amounts of creatinin in the urine. Also the exogenous factor (addition of meat extract) seems to be very small. In many a case of Basedow's disease there exists in addition a pronounced polyuria, that cannot be explained alone by the greater gram molecular amount [Molenmenge] of the urine on account of the increased metabolism. Here there is well present an excitation of the nerves of the renal vessels.

Later investigations, not as yet published, by *Zehner* and *me* as to the uric acid metabolism in Basedow's disease have led to a very remarkable result. We found in all the severe cases thus far investigated by us not only that the endogenous factor of the U-elimination was strikingly small, but that also the exogenous U-elimination was quite unusually small. I have reported such an investigation in Observation VIII, and would express the opinion that a portion of the uric acid is further decomposed under the influence of the hyperthyroidism.

There are found not rarely in Basedow's disease *ephemeral increases in temperature*. These were first described by *Bertoye*. Already *Charcot* had mentioned in opposition to *Bertoye* that they were very much less frequent than *Bertoye* stated. Among his numerous cases, they were never seen by *Kocher*. They have been seen however by *Sattler*. At all events, it is certain that in many cases of Basedow's disease the equilibrium of heat is very labile, and that on slight provocations the regulation is broken through in the sense of a hyperthemia. *Frederich Müller* saw regularly in one case marked rises of temperature after the administration of quinine. *Eppinger* and *Hess* saw them in cases after the injection of atropine. Moreover cases of peracute Basedow's disease are described that previous to death showed marked tachycardia with delirium, and a simultaneous rise of temperature to 40–41° C. (*Friedr. Müller*). Also *Hirschlaff* saw in a case a terminal rise of temperature to 40°. I have often seen in severe cases of Basedow's disease transitory rises of temperature to 39°, without finding a ground for them in the examination. After goiter operations, as is known, there have been observed marked rises of temperature that last for several days (*Bergert*, *Reinbach*, *Kocher*, *Lanz*). *Riedel* found them also after the operation for ordinary goiter, although those which occur after operations for exophthalmic goiter are essentially higher. *Kostlivy* found in all cases after operation pronounced neutrophilic hyperleucocytoses, but postoperative hyperthermia only with cases with thyrotoxic symptoms or in true Basedow's. *Kocher, Lanz, v. Bruns*, and *Schultze* explain this hyperthermia as an absorption fever, as in operations on the throat there are present especially favorable conditions for the formation of hematomata. More probable is the explanation that in consequence of the manipulation of the gland more thyroid secretion is absorbed and perhaps also the cervical sympathetic is irritated mechanically. The objection of *Schultze* that the injection of extracts from such strumas calls forth no essential rises of temperature in other people does not seem to me tenable, as normal individuals do not possess the lability of thermal equilibrium that exists in the Basedow's patients.

The **skin** in Basedow's disease is usually delicate, pliable, moist, readily reddened, showing well a lively play of the vasomotors. Increased sweat secretion is almost constant and is mostly present from the beginning of the disease. As do all the symptoms of Basedow's disease, the sweats undergo great variations; sometimes they occur only at night, and often they are influenced greatly by psychic excitations. In rare cases, the sweats have an odor (*v. Basedow', Dauscher*, Observation V, previously reported). Many of the patients sweat more on one side. In consequence of the abnormal moisture of the skin due to the sweats there is found in most Basedow's patients a reduction of the resistance to the passage of an electrical current; this was first described by *F. Chvostek* and *Vigouroux* and was more exactly studied by *O. Kahler*. On account of the marked excretion of sweat, miliaria ~~malaria~~ sometimes occur; the formation of larger vesicles with elevation of the epidermis, as in Case K. (Observation V), seems to be a very rare occurrence.

*Pigmentations* are found in about half of all cases, and indeed on the eyelids, lips, throat, on the lines of constriction of the corset laces, on the nipples, in the axillæ, on the linea alba, exceptionally on the mucous membranes, and also on the genitalia. In rare cases is found a diffuse brown coloration of the skin of the extremities, indeed even a bronzing. In many cases occur *edematous swellings*, especially of the eye-lids, but also on the extremities; they are firm and do not pit on pressure. They probably differ in nature. Trophoedemas are apparently not very rare in Basedow's disease. In many cases it seems as though we were dealing with a kind of lipodystrophy, as for example in the case reported by *v. Schrötter*, in which simultaneously with the emaciation of the upper half of the body there developed a considerable swelling of the lower half of the body, looking just like myxedema. Microscopical examination showed a lipomatosis with extraordinary large fat lobules. In this case there was found also a quite extraordinary pigmentation of the skin in the form of sharply circumscribed surfaces. I shall refer later, in the discussion of the pathogenesis, to the myxedematous swellings in this disease. There may be found also in certain cases hemorrhages into the skin and the mucous membranes. A common symptom in Basedow's disease is the falling out of the hair, that sometimes may lead almost to baldness. Also the nails are sometimes fissured.

Alterations of the **osseous system** occur mostly if the Basedow's disease has developed in an individual who is youthful. *Holmgren* has pointed out that youthful Basedow's patients show an accelerated growth in height and a somewhat premature closure of the epiphysial junctures. Very instructive is a case of *Schkarine* in a four and one-half-year-old girl who showed an abnormally rapid growth. Also *Ballet* reports a nineteen-year-old girl with Basedow's disease and "gigantism." The skeleton of the patient with Basedow's is mostly slender; the end phalanges are mostly pointed (*Revilliod*). *v. Jaksch* and *Rotky* describe in a case of Basedow's painful distentions at the distal ends of the forearm bones, and later also of the ribs, shoulder-blades, upper-arm, thighs, etc. Later the case developed kyphoscoliosis and paraplegia. The simultaneous occurrence of Basedow's and rheumatoid arthritis has been frequently described (*Jones* and *others*).

The alterations in the **genitalia** are mostly more pronounced in men, and in severe cases there may sometimes be decrease of libido and impotence. In women there are usually alterations of menstruation—sometimes cessation of menstruation is an early symptom. On longer duration of the disease there may come about an atrophy of the entire genital apparatus (*Cheadle*, *Askanazy*, *et al.*). In the case of *Kleinwächter* did there occur, in addition to a pronounced atrophy of the external and internal genitalia, even an atrophy of the mammæ. The relation between the genital sphere and the thyroid gland is found also in the fact, known for so long, that there is an increase of the volume of the thyroid at the time of puberty and during pregnancy. There may also occur during the period of pregnancy a development of a goiter (*Lawson Tait*) that disappears after labor and recurs during the next pregnancy. *Vermorel* refers the tachycardia and the cardiac palpitations that sometimes occur at the time of puberty to a light grade of hyperthyroidism. At any rate it is noteworthy from this point of view that Basedow's disease is not at all rare. During pregnancy the Basedow's symptoms mostly become exaggerated (*Cholmogoroff* and *others*). As further the tendency to Basedow's disease is sometimes inherited and in the decline of Basedow's patient frequently other diseases—neuroses of the vegetative nervous diseases, diabetes, etc.—occur, matrimony is to be advised against to Basedow's patients, or in it conception is to be avoided (*J. Novak*).

Basedow's disease can naturally be combined with many other diseases. Mentionable is the not rare combination with the trophoneuroses, especially with **scleroderma.** Such a case was first reported by *Leube*. Since that time numerous cases have been reported. An accurate compilation has been made by *Sattler*. Basedow's disease may be added to an already existing scleroderma, or sclerodermic symptoms may develop in the course of a Basedow's disease. It has often been observed that an improvement of the Basedow's disease is associated with an improvement of the scleroderma. There are, however, cases that take another course. Also complications of Basedow's disease with tetany have often been observed (see Chapter IV).

**Pathogenesis.**—Before I enter into the consideration of the individual forms of Basedow's disease, I should like to make a few remarks as to the *theory*. The observation of *Filehne* and of *Dourdoufi* and *Bienfait* that in animals after the transection of the corpora restiformia there occur tachycardia, exophthalmus and hyperemia of the thyroid gland (unilateral operations are attended with these phenomena on one side only) for a long time attracted many adherents to the bulbar theory that attributed all the Basedow's symptoms to alterations in the brain stem. Actually many symptoms point to a bulbar origin, as for instance the glycosuria that sometimes occurs, the alterations of the voice, and eventually the pareses of the various cranial nerves (*Sattler*). It is indeed true that in certain cases alterations are found in the medulla oblongata (*Mendel* and *others*), but in the majority of cases these findings are absent. The French school, especially *Charcot*, *Trousseau* and *Gauthier*, and in Germany *Gerhardt* and *Buschan*, have regarded Basedow's diseases as a neurosis, in that they assume that the entire nervous system is diseased. Then *Möbius*, as has already been mentioned in the beginning, placed the thyroid gland as the central figure in the pathogenesis, assumed a poisoning of the body by the copious production of a harmful secretion, and expressed the thought that all forms of Basedow's disease (goiters that have become associated with Basedow's symptoms, formes frustes, and the fully developed Basedow's disease) all depend on a uniform basis. *Möbius* first pointed out the opposition between the symptom picture of Basedow's disease and the disease condition that ensues after extirpation of the thyroid gland. *Möbius's* teaching gained ground rapidly, in that the predominant place of the thyroid gland in the pathogenesis of Basedow's disease found general recognition; but on the contrary the views as to the kind of functional disturbance diverged greatly. The view first advocated by *Notki* and later by *Blum*, that certain poisons existing in the body were rendered nontoxic (*i.e.*, detoxicated) in the thyroid gland and that in Basedow's disease this detoxication is incomplete, may to-day be regarded as untenable. It was displaced by the secretion theory, which maintained that from the thyroid gland a specific active secretion is given off to the blood path which is necessary for the retention of certain body functions, or, according to the supposition of others, to the paralyzing of certain poisons circulating in the body. In the last-mentioned view again greets us the detoxication theory, although in an essentially modified form. In this form, however, there is as little evidence for it as in its older form. The known experiment of *Reid Hunt*, according to which the resistances of animals to methyl cyanide is somewhat raised, is not evidence for the detoxication theory as, as *Reid Hunt* himself emphasizes, the heightening of resistance can be called forth by the heightening of the metabolic processes that ensues in consequence of the administration of the thyroid.

*Oswald*, *Minnich*, and *others* assume that in Basedow's disease the thyroid furnishes a less active secretion (hypothyrosis or dysthyrosis); *Möbius* believes, as already mentioned, in the increased secretion of a substance that is qualitatively altered; while most authors, especially *Fr. Kraus*, advocate the mere increase of the thyroid function without qualitative alteration (hyperthyroidism). For this supposition, which I also advocate, speaks:

1. The opposition in the symptom picture of Basedow's disease and myxedema.
2. The fact that on exothyropexy (conduction of the secretion of the thyroid gland to the exterior) the thyroid gland in Basedow's disease furnishes more secretion than the thyroid of the ordinary strumas.
3. The results of surgical treatment (diminution of the secreting parenchyma).
4. The aggravation of Basedow's disease on the administration of thyroid glandular substances and finally,
5. Artificial thyroidism.

Against these points many objections have been raised of which I shall mention only the most important. Against point 5 has been objected that it is true that most of the symptoms of Basedow's disease may be produced on the administration of thyroid gland, but that these remain much behind those of true Basedow's disease in intensity and that some, for instance the eye symptoms, are not produced in artificial thyroidism at all. As far as the eye symptoms are concerned, I must again mention that *Kraus* and *Friedenthal* observed exophthalmus after the injection into the blood of rabbits of the thyroid glandular juice contained in the serum, as did *Heinecke* on long-continued treatment with large amounts of thyroid glandular substance; especially, however, that to-day exophthalmus can be produced in dogs on the use of juice expressed from human strumas (*Lampé, Liesegang*, and *Klose, Baruch*).

*Lampé, Liesegang* and *Klose*, on the intravenous injection into certain breeds of dogs of fresh juice expressed from Basedow strumas, have found marked increase of the temperature and pulse rate, exophthalmus, glycosuria and albuminuria. Death occurred in convulsions. Expressed juices that were obtained from normal thyroid glands or ordinary strumas had no effect, or very little effect. The authors regard these experiments as evidence that in Basedow's disease there exists no hyperthyroidism but a dysthyroidism. The experiments are very significant, but I do not regard them as furnishing evidence for a dysthyroidism. It will not do to leave altogether unconsidered the long-known fact that, as stated above, through the feeding with normal thyroid glandular substances all the symptoms of Basedow's can be produced in a more or less well-pronounced manner. Also

*Baruch*, who experimented in a manner quite analogous to that of *Lampé, Liesegang*, and *Klose*, and had similar results, does not agree with these authors' interpretation.

Much cited is the case of *v. Nothafft*, which I shall describe in detail on account of the interest that it has attracted. It was that of a forty-five-year-old man with a corpulency that had been increasing for several years. In the course of about five weeks he took almost 1000 thyroid-gland tablets. In a short time there developed a complement of Basedow's symptoms of which I will mention irritating cough, tachycardia, acceleration of respiration, slight increase of temperature, bilateral exophthalmus, tremor of the whole body, even of the tongue, increased strangury, glycosuria (up to 1 per cent.), morose mood, excitement, and finally swelling of the thyroid gland. The irritating cough disappeared eight days after the onset of the thyroid glandular therapy, as did also the sugar, without alteration of the diet; the tremor disappeared after four weeks; the struma, the exophthalmus and the rest of the eye signs lasted nearly one-half year and then retrogressed almost entirely. Although in this case almost the entire symptom-complex of Basedow's disease developed, it is however not entirely convincing. We shall see later that in many persons, often relatively small amounts of iodine are sufficient to occasion an enormous increase of the function of the thyroid gland. Also in the case of *Nothafft* the amounts of iodine contained in the thyroid gland material administered may have sufficed for the purpose, as speaks also the transitory development of a struma. This objection could indeed be mostly made in hyperthyroidism, unless the thyroid gland in the affected individual was absent. Now in myxedema after thyroid operation we may indeed frequently observe an extraordinarily high tolerance for thyroid-gland substances, but on the other hand, symptoms of hyperthyroidism may be elicited on the administration of enormous amounts. At all events, it must not be forgotten that we do not know anything as to the amount of thyroid-gland secretion given off to the blood in Basedow's disease. Probably it is very large. We should further consider that on the peroral administration of large amounts the absorption would soon suffer harm.

Although I therefore do not recognize the arguments advanced up to the present time as convincing, I shall have to acknowledge that artificial thyroidism has not as yet furnished complete evidence for the opinion here advocated. *The greater intensity of the symptoms in true Basedow's always admits of the possibility that hyperthyroidism is only a partial phenomenon of an alteration of the central nervous system and that the organism of the Basedow's patient reacts to hyperthyroidism in a different manner than the normal. The foundation for this can perhaps be seen in a constitutional alteration, of which the cause lies in the associated involvement and perhaps in a functional increase of other ductless glands. The final cause of all the manifestations could well be regarded as lying in the central nervous system.*

It has been pointed out that the multiplicity of the Basedow's symptoms cannot well be explained by the functional increase of the thyroid gland alone, and that therefore also on this ground a qualitative alteration of the secretion must be supposed. This objection does not hold in this general interpretation. All the symptoms of Basedow's disease may be produced, at least in miniature, on the administration of normal thyroid gland. What syndrome will develop all depends on the constitution of the affected individual (*Falta*, *Newburgh*, and *Nobel*).

Objections have been raised to point 4. It is true that in the most cases we observe under thyroid medication distinct aggravation of the Basedow's symptoms, such as increase of the tachycardia, arrhythmia, sleeplessness, excitement, profuse sweats, gastrointestinal disturbances, severe prostration, etc. But there have even been reported cases in which the thyroid medication acted favorably. Quite complicated theories have been advanced for the explanation of these cases; thus, for example, *Möbius* believes that the increased activity of the thyroid gland retrogresses if through the administration of thyroid glandular substance one gives it time to recover itself. Such cases may be explained without overdrawing by the observation that in many cured cases of Basedow's disease the counter-regulations develop strongly. I previously mentioned a case in which, after the cure of the Basedow's, even large quantities of thyroid-gland tablets would bring forth no distinct relief. If, therefore, thyroid medication takes place in the declining stage of the disease, slight favorable results may be assumed thereby.

The most important point is point 1, the opposition in the symptom picture of Basedow's disease and of myxedema. I here reproduce the excellent table of *Kocher:*

| Cachexia Thyreopriva | Morbus Basedowi |
|---|---|
| Absence or atrophy of the thyroid gland. | Swelling of the thyroid gland—mostly of a diffuse nature, hypervascularization. |
| Slow, small, regular pulse. | Frequent, often tense, rapid, now and then irregular pulse. |
| On application of cold to the skin, all vasomotor changes are absent. | Extraordinarily irritable vascular nervous system. |
| Listless quiet gaze without expression and animation. | Anxious, unsteady gaze which is choleric on fixation. |
| Narrow palpebral fissures. | Wide palpebral fissures, exophthalmus. |
| Retarded digestion and excretion, poor appetite, few demands. | Abundant evacuations, mostly abnormal appetite, increased demands. |
| Slowed metabolism. | Increased metabolism. |
| Thick, nontransparent, folded, dry to scaly skin. | Thin, transparent, finely injected, moist skin. |
| Short, thick fingers often broadened at the ends. | Long, slender fingers with pointed end phalanges. |
| Sleepiness and tendency to sleep. | Sleeplessness and disturbed sleep. |

| Cachexia Thyreopriva | Morbus Basedowi |
|---|---|
| Deficiency of thoughts, listlessness and loss of emotivity. | Accelerated sensation, apperception and action. |
| Retarded sensation, apperception and action. | Flight of thoughts, psychic excitement as far as hallucination, mania and melancholia. |
| Awkwardness and clumsiness. | Constant unrest and haste. |
| Stiffness of the extremities. | Trembling extremities, increased mobility of the joints. |
| Remaining behind of bone growth—short and thick, often deformed, bones. | Slender skeletal build, now and then weak and thin bones. |
| Constant feeling of cold. | Unbearable sensation of heat. |
| Retarded, heavy breathing. | Superficial breathing with deficient inspiratory expansion of the thorax. |
| Increase of body weight. | Reduction of body weight. |
| Senile appearance, even when the patients are young. | Youthful luxuriant body development, at least in the initial stages. |

*A. Kocher* distinguishes, in addition to these opposed symptoms, symptoms that are similar in both diseases and reckons under these certain forms of edema, dryness and becoming gray of the hair, pigmentations, and the diminution of the secretion of the salivary and lachrymal glands that is observed in many cases of Basedow's disease. One may also count with these symptoms the dryness of the skin seen in rare cases of Basedow's disease and the glycosuria of quite rare cases of myxedema. These "exceptions to the rule" will hardly suffice to limit essentially the opposition in the symptom picture of the two conditions. For the explanation of many of these exceptions, constitutional differences may be called into account; for example, for the explanation of the dryness of the hair and of the skin and the diminution of the salivary secretion. *Eppinger* and *Hess* regard the cause of the opposed behavior of the sweat formation in different cases of Basedow's disease as a different tonus of the sympathetic or of the autonomous nerves; surely from such behavior cannot be based an argument against the hypothesis of hyperthyrosis, because also in artificial hyperthyroidism we saw, in certain cases, a diminution of the sweat formation under the influence of the thyroid medication. As far as the behavior of the hair is concerned, it must be mentioned that in Basedow's disease the hair indeed may be dry but is also thin, while in myxedema it tends to be thick, loose, and brittle. The explanation of other "similar" symptoms may be attributed to the pathological correlations; for instance, the rare glycosuria in myxedema may well point to a simultaneous insufficiency of the pancreas. I would enter more fully only into a discussion of one of the symptoms detailed, as it is regarded by the adherents of dysthyrosis as an especially important argument. It is the combination of Basedow's and myxedematous symptoms in the same patients. In *Sattler's* work will be found a compilation of such cases. The observation that a fully developed Basedow's may gradually go over into a myxedema has nothing striking about it, for an overfunctionating thyroid may degenerate and become functionally insufficient. Such a case was first described by *Joffroy* and *Achard.* In a twenty-three-year-old woman there first developed a typical Basedow's disease, then great weakness, swelling of the feet, legs, trunk, the upper extremities and the face, apathy, great fatigability. Autopsy showed a sarcoma of the pleura and disappearance of the thyroid parenchyma, in the place of which was found connective tissue. Confer also the case of *Gauthier.*

Concerning the cases with simultaneous occurrence of Basedow's disease and myxedema, I would remark that in many of these cases the diagnosis myxedema seems to me very doubtful indeed. I call to mind the above-mentioned case of *v. Schrötter*, that microscopical examination showed to be lipomatosis. Perhaps something analogous is to be seen in the case of *Hirschl*, in which the skin of the ankle-joint was entirely normal and the swelling of the leg ended in a sharp ring. Also the swelling of the face was limited to a pad-like thickening on the lower border of the lower jaw. The circumstance that the skin was dry is no evidence for myxedema; otherwise there was a typical Basedow's disease. Also in both of *Loew's* cases—otherwise typical cases of Basedow's disease—there existed a thickening of the extremities that involved the backs of the feet only little if at all. Thyroid medication had no influence on this thickening.

It seems to me further noteworthy that almost all the cases that *Sattler* quotes show peculiar complications. In two cases (cases of *Möbius* and of *Hirschl*) there existed at the same time osteomalacia. In the case of *Sollier*, the myxedematous swellings occurred especially at the time of menstruation, in the case of *Ulrich* there were choreiform twitchings, in the case of *Kowalewsky* epilepsy since youth, in the case of *Holub* there was marked *Chvostek's* sign, and in *Osler's* case there later occurred under thyroid medication marked glycosuria. Moreover, I consider it possible that cases that stand on the border-line of thyroid glandular insufficiency would under certain conditions show lowered tolerance for thyroid-gland preparations. As example I cite the following case:

*Observation X.*—Mrs. B., forty-eight years, has had five confinements. After the last confinement there was a gradual taking on of body weight, until she weighed about 125 kg. About twenty years ago she underwent a reduction cure, in the course of which she rapidly lost 14 kg. At the time, also, thyroid-gland tablets were administered. After the treatment marked excitability, cardiac oppressions, diarrheas, sweats, and tremor occurred. These symptoms lasted a long time. Then they retrogressed and the body weight again increased. Three years ago after inunction of an iodine salve, a gradual increase of the Basedow's symptoms took place. The thyroid gland had formerly been large, and now enlarged still more. Two years ago the right lobe of the thyroid gland was extirpated. After the operation there was gradual increase of body weight, about, 12 kg., sensation of cold (can scarcely warm herself), skin dry and cold, mental sluggishness, constipation. For several months thyroid medication. The skin again became moist, cardiac manifestations, tachycardia, and arrhythmia again appeared, the patient was excited, the constipation disappeared. Body weight decreased. When the thyroid medication was discontinued, the weight increased again and the myxedematous symptoms reappeared. Since that time, periods of thyroid administration were many times introduced, and regularly after the use of only two to three tablets a day for a short time Basedow's manifestations appeared. At present, after a three weeks' thyroid treatment, there is a slight tachycardia and especially marked arrhythmia. The heart is dilated, the pulse is poorly filled, the skin is moist, there are stary eyes and a very slight fine-waved tremor.

Later, in the chapter on myxedema, I shall cite similar cases. The slight tolerance toward thyroid preparations is in this case certainly remarkable, as high tolerance is characteristic for typical cases of myxedema. To my mind there is in this case no necessary basis for the assumption of a dysthyrosis. It is well known that a degenerated heart muscle is extraordinarily sensitive toward thyroidin. It can very well be conjectured that a slight excess of thyroidin would already damage the heart muscle, if the myxedematous symptoms have not as yet altogether disappeared. Finally, it remains to be investigated whether in similar cases the myxedematous swellings of the skin are always dependent exclusively on the thyroid glandular insufficiency. Much speaks for the fact, as above indicated, that in such cases frequently also other ductless glands are degenerated. Especially frequent there occurrs a simultaneous affection of thyroid and hypophysis. As is known, there is found an insufficiency of the pituitary gland, alterations of the skin and trophic disturbances that are similar to those of myxedema. I regard it as very likely, in many Basedow's cases with myxedematoid symptoms, and in cases of myxedema that react to thyroid treatment with only partial improvement and even show signs of hyperthyroidism rapidly, that these myxedematoid manifestations depend on a hypophysial insufficiency (see also the chapter on the hypophysis).

Many authors are disposed to ascribe to thymus hyperplasia an important rôle in the pathogenesis of Basedow's disease. Already *v. Hansemann* was of the opinion that the cases of "thymus Basedow" could be distinguished also clinically. *Hart* refers the cardiac manifestations in Basedow's disease to the thymus hyperplasia alone and sees in such cases thyroid hyperplasia as something secondary. Reversely, *Gebele* regards the enlargement of the thymus gland as a compensating process that serves to weaken the hyperthyroidism. Especially worthy of notice are the reports of *Garré* and *Capelle* and *Bayer*, concerning the extirpation of the thymus gland in Basedow's disease. In the case of *Capelle* and *Bayer*, thymectomy seemed to have no influence on the struma, the exophthalmus, or the bulbar symptoms, but the cardiac symptoms seemed to improve. After some weeks the mononucleosis had disappeared. *Gebele*, however, does not regard the thymus in this case as enlarged, and points out that five months after the thymectomy an operative procedure on the thyroid was necessary on account of pronounced symptoms of Basedow's. According to *E. Bircher*, implantation into the abdominal cavity of dogs of thymus gland that came from an individual who died from thymic death at operation called forth temporary tachycardia, conditions of excitement, and tremor, and also a struma developed in these animals. What exists clinically and experimentally as to this subject seems to me far insufficient to ascribe to the thymus gland so great a significance as to warrant the delimitation of a thymogenic Basedow's.

Yet a few words as to the place of **iodine** in the physiology and pathology of the thyroid gland. Iodine is found in very many organs, as in the skin, the lungs, the ovaries, the small intestines, the blood, the liver, the bile, the hairs, and in the glandular part of the hypophysis (*Blum*, *Bourget*, *Heffter*, *Drechsler* and *others*). The iodine-contents of the thyroid gland is, however, much larger (according to *Justus* eight to ten times) than that of the other organs relatively rich in iodine. The normal thyroid gland of man contains according to *Magnus-Levy* about 0.3–0.9 mg. of iodine for 1 kg. of dry substance. The entire gland contains about 2–9 mg. (*Baumann*, *Oswald*). The thyroid glands of fetuses and new-born children are iodine-free. The thyroid glands of herbivora have very high iodine-contents, while the thyroid glands of carnivora have the lowest iodine-contents (*Baumann*, *Roos*, *Oswald*). Copious feeding of meats to dogs makes the thyroid gland very poor in iodine. The activity of the thyroid glandular substance is bound with its iodine-contents and parallels these. As is known, all the symptoms of deprivation after extirpation of the thyroid gland may be alleviated by the administration of iodine-containing thyroid glandular substance. The iodine-containing albuminous substances obtained by *Oswald* from the thyroid gland, iodthyroglobulin, contains about 1.75 per cent. of iodine. The iodothyrin obtained by *Baumann* by splitting with acids contains about 9.3 per cent. *Oswald* obtained from thyroglobulin by splitting with acid a still richer iodothyrin with 14.29 per cent. of iodine. While the iodthyroglobulin seems to possess the complete action of dried thyroid-gland substance, iodothyrin is less active, even though it possesses a greater heightening power on metabolism and a greater action on the cardiovascular apparatus than artificially iodized albuminous bodies. Its action is, however, much less than that of dried thyroid glandular substance. While, for example, we could obtain with 2.7 gm. of *Bourrough, Wellcome, and Co.'s* tablets distinct tachycardia and other slight symptoms of thyroidism in three days, later twenty-one *Bayer's* iodothyrin tablets daily, administered for a long time, were without effect (experiment of *Dr. Fleming*). The iodothyrin is also incapable of alleviating the manifestations of deprivation that occur in youthful animals after thyroidectomy (*Pick* and *Pineles*). Just as after splitting with acids, the thyroid-gland substance, after exposure to digestive ferments, loses in activity. Exposure of short duration to peptic and tryptic digestion does not seem to alter the specific substances, as we are able to bring about the complete action even on peroral administration. All experiments point to the fact that the thyroid gland carries iodine in a specific organic combination, perhaps iodthyroglobulin.

The iodine-contents of glands altered pathologically varies greatly. The purely parenchymatous Basedow strumas contain almost no iodine; strumas rich in colloid are also rich in iodine. Investigations by *Oswald*, *A. Kocher*, and *others* have shown that the iodine-contents of strumas rich in colloid is really not absolutely greater than in the normal thyroid-gland, but that relatively, that is, taken in relation to the amount of thyroid gland substance, it is less. On the contrary, the holding in thyroglobulin is absolutely and relatively greater; in colloid goiters there is found, therefore, either an iodthyroglobulin poor in iodine or less iodthyroglobulin and more thyroglobulin. Probably in the Basedow struma the formed iodthyroglobulin reaches the circulation immediately in consequence of the increased permeation with blood.

The function of the thyroid gland, if the organ is altered pathologically, may be influenced by the administration of inorganic iodine. Individuals with normal thyroid glands separate out again the excess of iodine rather promptly, without any disturbance of the iodine equilibrium. Strumous individuals, according to the investigations of *A. Kocher*, behave very diversely; in strumas with abundantly functionating parenchyma more iodine is excreted than is introduced, so that thyroid-gland tissue is melted down and symptoms of thyroidism may appear. In strumas with relatively iodine-poor colloid this is first iodized; there therefore occurs an iodine retention, but on continued treatment with iodine there may come about melting down of the colloid and thyroidism. Administration of the phosphates should favor the action of iodine and keep back the melting down of tissues. This experiment renders intelligible the old experience that in certain forms of struma the administration even of very small amounts of iodine leads to manifestations of thyroidism.

*Kocher's* investigations stand in the most intimate relation to the more older experience as to the so-called iodine Basedow's. *Coindet*, in Geneva introduced iodine into therapy in 1820. Shortly afterward it was reported by *Coindet* himself and by *Gautier*, *d'Espine*, *Relliet*, and *others* that after the administration of iodine there often occurs a series of symptoms that are sharply distinguished from those of pure iodism (acne, catarrh of the mucous membranes, etc.). These symptoms (tachycardia, tremor, emaciation, etc.) could develop in strumous individuals after the administration of mimimal amounts of iodine, and long outlast the medication. Already *Lebert* advocated the opinion that in such cases the administration of iodine led to rapid absorption of thyroid glandular substance and the symptoms mentioned could be referred to this. *Breuer* explained the contradiction that these observations met with in Paris by the fact that only certain forms of struma, as those for example in Geneva or Vienna, reacted to the administration of iodine in this manner. The regional difference in the sensitiveness toward iodine can be elicited from the large series of experiments of *Fleischmann*. *Fleischmann* after the administration of iodine to the persons under investigation in Basel saw acceleration of the pulse in 68 per cent., in Berne in 23 per cent., in Berlin in only 3.7 per cent. Also in Heidelberg was the use of iodine warned against by *Krehl*. According to the statement of *Breuer*, *Kocher*, *Möbius*, *Ortner*, *Goldflam* (the last on the injection of iodipin into a person with tabes), there may develop even a typical morbus Basedowi, also in cases in which no struma existed before the treatment with iodine; or in cases of cured Basedow's there may occur a severe relapse with a new enlargement of the thyroid gland. Case B. (Observation X), previously reported, furnishes a good example of this; or an existing Basedow's disease may be considerably aggravated by iodine therapy (compare case S. *Schm*). In Vienna, according to my observations, conditions are such that one must directly warn young persons with diffuse soft strumas against the use of iodine. *Pineles* has especially frequently seen the occurrence of the manifestations of thyroidism in goitrous individuals in families in which Basedow's disease or diabetes has occurred or in which a neuropathic disposition has existed, after the use of iodine, often in a minimal amount.

It would really be correct to separate the cases of simple iodthyroidism from those of iodine Basedow, although there are transitions between the two groups. In the first group of cases administration of iodine brings about a rapid melting down of thyroid-gland tissue and hence the manifestations of thyroidism. After the discontinuation of the iodine medication the manifestations for the most part rapidly retrogress, the thyroid gland remaining the same in size or becoming smaller. In the cases of iodine Basedow, on the contrary, the thyroid gland increases in volume, and the Basedow's manifestations can long outlast the iodine medication.

As to the **etiology** of Basedow's disease we do not know anything definite. The *goiter noxus* can play only a subordinate rôle, as just the fully developed forms of Basedow's disease are rare in goiter districts. *Neuropathic predisposition* is to be regarded at the most as a predisposing factor; psychic and bodily *traumata* as well as iodine and thyroid glandular medication are to be regarded as determining factors. Frequently Basedow's disease develops at the close of *acute infectious diseases* (acute articular rheumatism, angina, typhoid fever, scarlet fever, etc.). In some cases an idiopathic thyroiditis passes over into it. Finally, it should be mentioned that *Kahn* and *myself* in several cases of declining tetany saw occurrence of thyroid glandular swelling and distinct Basedow's symptoms. As further the true Basedow's struma shows accumulations of lymphocytes and as the parathyroid glands in such cases are swollen, many authors have thought of an infectious etiology of Basedow's disease. This assumption is not however satisfactory, as many cases of Basedow's disease develop in complete health and are entirely fever-free. Hence the acute infection is regarded by *Möbius*, *de Quervain* and *others* only as the connecting link. As I have already mentioned, the assumption of a thymogenic Basedow's disease seems to-day to have but little foundation. Also those who refer all the symptoms of Basedow's disease to an increase of function of the thyroid gland must recognize that the *cause proper* of this increase of function is as yet unknown. As the secretion of the thyroid gland is regulated by the central nervous system, so lately nervous centers have again been assumed (*Wiener*), thus an approach again being made to the bulbar theory of *Charcot* and *Geigel* (*Oppenheim*). According to this theory many of the Basedow's symptoms, before all the eye symptoms so hard to produce by artificial thyroidism, are coordinated with those of the thyroid glandular swelling. This theory would at least explain the rare observation that the exophthalmus may occur unilaterally (*Fr. Müller*, *Roasenda*, *Kocher*, and *others*).

The statements as to the theory and etiology of hyperthyrosis allow to be recognized the fact *that the cause of Basedow's disease is not as yet explained. Most of the symptoms can be referred to the hyperthyroidism; the cause of the hyperthyroidism is possibly conditioned centrally, and thus perhaps a series of symptoms and alterations in the function of other ductless glands are coordinate with the hyperthyroidism.* Finally, we should point out the not rare combination of symptoms similar to those of Basedow's disease and even typical hyperthyrosis with trophoneuroses (scleroderma) that obtain some value in this connection (see Chapter I).

**Forms of Basedow's Disease.**—In consequence of the great variability which Basedow's disease presents in its manifestations and in its course, there has existed from far back the attempt to bring forward certain symptoms as cardinal symptoms and to lend to certain apparently more remote symptoms a greater nosological independence. Originally the symptoms of the so-called Merseburg triad—exophthalmus, goiter, and tachycardia—were taken as the cardinal symptoms. However, exophthalmus is wanting in a not inconsiderable part of the cases of this condition and, moreover, *Pierre Marie* added a new cardinal symptom—the tremor. The fact that the exophthalmus is often permanently absent led *Pierre Marie* to the establishment of the formes frustes, the effaced, or better, the incomplete forms, while formerly *Charcot* understood by forme fruste the residual condition after improvement of the classic form. *Gautier* and *Buschan* distinguished true Basedow's disease and the pseudo- or secondary Basedow's disease, regarding the former as a general neurosis with the predominance of the psychic and vasomotor sphere, while the latter is brought about by other changes in the organism among others also a disturbance of function of the thyroid gland. *Möbius* distinguished primary and secondary Basedow's disease according as to whether the alteration of function developed in a previously normal or in a goitrously degenerated thyroid gland. Secondary Basedow's disease ordinarily pursues a chronic course and is often incomplete; the primary is often acute and rich in symptoms. The secondary form corresponds to the gôitre basedowifié (*Revilliod* and *Pierre Marie*). *Möbius* does not however ascribe so very great a significance to this distinction, as he regards the alteration of function of the thyroid gland as the central figure. "The cardinal symptom is just the tachycardia." *Th. Kocher* distinguishes between the fully developed forms and the so-called hyperthyrotoxic equivalents.

*Fr. Kraus* has separated out the so-called goiter heart as an especial independent form. Apart from those cardiac disturbances which come about through mechanical obstruction to the circulation or respiration, there exists additionally in goiters, according to *Kraus*, a cardiac disturbance produced by action at a distance of the thyroidal secretion that is associated with other hyperthyroidal symptoms.

*Eppinger* and *Hess* distinguish between sympathicotonic and vagotonic forms, according to whether the symptoms of excitation predominate on the part of the autonomous or of the sympathetic nerves. Characteristic for the vagotonic cases would be "a relatively slight degree of tachycardia, with however markedly pronounced heart oppressions, distinctly marked *v. Gräfe*, and wide palpebral fissures, absent *Möbius*, slight protrusion of eyeballs, the marked secretion of tears, outbreaks of sweats, diarrheas, distresses that are to be referred to hyperacidity, eventually eosinophilia, and disturbances of the rhythm and mechanism of respiration, absent alimentary glycosuria;" in the sympathicotonic cases, *Eppinger* and *Hess* found "marked protrusion of the bulbs, greatly increased cardiac activity with slight accentuation of the subjective disturbances, absence of sweats and diarrheas, marked falling out of the hair, inclination to increase of fever, absence of eosinophilia, no disturbances of respiration, alimentary glycosuria."

The position of many of these symptoms as sympathicotonic or vagotonic is as yet quite insecure. Thus, for example, the interpretation of the sweats as vagotonic is not sufficiently founded, because as yet we have known nothing as to the course of autonomous nerves of the skin. The significance of the individual phenomena is rendered the more difficult because there exist both sympathetic accelerator [fördernde] and inhibitor and autonomous accelerator and inhibitor fibers. I cannot look upon the alimentary glycosuria as sympathicotonic, as according to our investigations the alimentary factor is to be sharply separated from the nervous factor and for the former the functional breadth of the pancreas is the determining factor. Moreover, there are undoubtedly cases, as *Eppinger* and *Hess* and recently *v. Noorden, Jr.*, bring out, in the course of which at times the sympathicotonic, at times the autonomotonic, symptoms predominate. Before everything else, however, is the tachycardia evidently to be regarded as the cardinal symptom of Basedow's disease and, on the other hand, the sweats or the marked moistening of the skin is so extraordinarily frequent that almost never can we speak of a purely sympathetic type in the sense of *Eppinger* and *Hess*. In my opinion everything speaks for the fact that in Basedow's disease the *entire nervous system* is in a condition of overexcitement and that the pictures presented by the vegetative nervous system are as uncommonly manifold and always changing.

Very recently *Stern* has entered the list for the greater independence of certain forms of Basedow's that he regards as Basedowoid. In a certain sense there is in this a reversal to the views of *Gautier* and *Buschan*. Stern divides the classic form into true and degenerative Basedow's disease, according to whether the disease develops in a previously normal or in a neuropathic individual. From the great group of formes frustes *Stern* separates out *Kraus's* goiter heart; the remaining forms are based regularly on an original degenerative neuropathic foundation. Basedowoid and Basedow's according to this view are distinguished from each other essentially by their beginning, course, and prognosis. According to *Stern*, they never pass over into each other. *Chvostek* agrees with *Stern* on the whole, except that he would regard as formes frustes the relatively abortive cases of true Basedow's that pursue a light course. *Langelaan* regards *Stern's* Basedowoid as Basedow's on an asthenic basis. The practical significance of a clinical differentiation of the individual formes is in themselves intelligible if through them deductions as to the prognosis and therapy can be given. On the other hand, I would point out with emphasis the danger that exits in the fact that through the accentuation of the distinguishing features, the painstakingly wrought-out conception of the pathogenetic unity, the hyperthyroidal syndrome is relegated too much to the background. The same is true as to the statement as to which symptoms must be present, if we wish to establish the diagnosis of hyperthyrosis, that is, Basedow's disease in a wider sense. It seems to me suitable for the explanation of this question to go the other way about, *and to establish what symptom or what symptoms are constant in artificial thyroidism and the earliest to appear*. According to our investigations on this subject it appears that without doubt the cardiovascular symptoms, especially the tachycardia, here predominate. To the tachycardia may be added sweats, or mononucleosis, or psychic excitability, or headaches, etc. The symptom that occurs twice as frequently is according to our observation the greater moisture of the skin, which is absent only in rare cases. If other symptoms are added to this, we obtain syndromes such as tachycardia, sweats, headaches, or tachycardia, sweats, tremor, or tachycardia, sweats, mononucleosis, etc. Hence by this route we come back to the conception of *Charcot* and *Möbius that just cardiac or vascular disturbances are to be regarded as the cardinal symptom*, to which is added in most cases the increase in metabolism; with somewhat longer action of the hyperthyroidism, tachycardia, mononucleosis, and tremor may well be regarded as cardinal symptoms. From these symptoms to pronounced exophthalmus is indeed a wide stride; probably there is added an enormous flooding of the blood with thyroid secretion; and perhaps is necessary for it other constitutional factors whose nature is unknown to us. *In the fully developed cases we have always before us a marked condition of excitation of almost the entire vegetative nervous system.* This way of looking at the subject brings us back to *Möbius's* view that all the syndromes of Basedow's disease have a common nucleus. The classic form of Basedow's is characterized only through the more pronounced accentuation of the eye symptoms, through a more considerable increase of the metabolic processes, and through its rapid origin, while *Stern's* Basedowoid ordinarily shows from the beginning an insidious course.

From both these forms—the classic form and the forme fruste—is to be delimited sharply only the *Kraus-Minnich* goiter heart. The newer investigations show that here the cardiac disturbances are not of pure hyperthyroidal origin, but that the goiter noxus is involved in their coming about. I shall therefore speak of this form under cretinic degeneration.

**Course.**—The classic forms of Basedow's disease as well as the formes frustes show the greater variability in their course. The classic form may develop in the midst of complete health, often in a peracute manner, for example, during swimming (*Přibram*) or a few hours after a tonsillotomy (*Patterson*); the condition may again return to normal, with a disappearance of the eye symptoms, or may lead to death under stormy manifestations (delirium, premortal increase of temperature), or may go over into a chronic form with remissions and renewals. It can also after several years show a surprising turn toward amelioration, and may eventually heal with the retention of the exophthalmus, which has now become definite; relapses of this form are frequent; in other cases it leads to severe irreparable cachexia. The classical form may also begin gradually both in previously normal and in neuropathically affected individuals, may also show quite the picture of a forme fruste, and only later develop fully under any determining factor or without ascertainable cause.

Among the formes frustes are slight abortive cases of sudden onset. The cases with fat stools and glycosuria are mostly cases of abortive formes frustes (without eye symptoms). Many of the cases that I observed set in after trauma, but in the great majority of formes frustes a quite gradual beginning is the rule; especially in those forms existing on a neuropathic basis, the forms that *Stern* designated as Basedowoid, the beginning goes as far back as youth, and decades may lapse before the disease is to any degree distinct. In such characteristic cases the trophic disturbances are markedly prominent. It is *Stern's* great service to have shown that in these cases there is quoad sanationem a very favorable prognosis. On the contrary I cannot agree with *Stern* that "Basedowoid" cases never go over into the classic form of Basedow's. It seems to me that the typical Basedow's on a degenerative foundation (*Stern's* degenerative Basedow's) can hardly be anything else than a Basedow's with acute exacerbations.

The **diagnosis** of the classic form is easy, differential diagnostic difficulties presenting only in the formes frustes. *Alcoholism* and *nicotinism* may produce tachycardia and tremor; the history or finally the demonstration of a central scotoma will set the diagnosis right (*Chvostek*). *Fr. Müller* has pointed out the similarity of chronic *lead poisoning* to the formes frustes. Here the lead line and the granular erythrocytes will set matters clear, although I have seen a case of the combination of the two conditions [lead poisoning and Basedow's]. Difficulties may also attend the decision of the question whether such Basedow's symptoms as tachycardia, pigmentations, lability of the vascular system that often accompany such trophoneurosis of the vegetative nervous system as scleroderma, depend on a simultaneous hyperthyrosis or the fundamental disease as such. *Cassirer* further points out that a slight grade of exophthalmus is often simulated by the sclerodermic mask. The presence of a Basedow's struma in four such cases enables us to speak with probability of a combination with Basedow's disease. Most difficult is the differential diagnosis from the *cardiovascular neurosis* of *Chvostek* in which occur tachycardia, dermographism, inclination to sweats and fine-waved tremor. Great lability of the heart manifestations speak for neurosis, enlargement of the thyroid gland and slight eye symptoms, heightening of the [metabolic] exchange (*v. Noorden*) and especially a mononucleosis speak for hyperthyroidism. In many cases, as *Chvostek* emphasizes, a certain diagnosis can be first established from the course of the disease. In persons that come to the physician with complaints as to slight emaciation, nervousness, cardiac palpitations and psychic excitation, light will often be thrown on the matter by the fact that they have been using iodine. For the judgment as to fat stools is the evacuation of unsplit neutral fats and the predominance of finely divided soap balls and fatty acid needles decisive. Evidence for the diagnosis of a complicating glycosuria is afforded by the fact that the true thyrogenic glycosuria usually is of slight intensity and that with the improvement or the retrogression of the Basedow's symptoms it not only disappears, but high or normal tolerance for carbohydrates reappears very rapidly.

**Prognosis and Treatment.**—Since the beginning of the operative era in the treatment of Basedow's disease the question of especial interest has been whether surgical treatment should supersede the medical treatment. In consideration of the great variability in the course of Basedow's disease it is intelligible that this question can be solved only by a great statistical material. We must therefore bring up the question as to what prognosis belong to the cases of Basedow's disease treated purely medically. The greatest difficulty lies in the fact that on the part of the internist only the severest, because interesting, cases are published, and that further this material comes especially from clinics and dispensaries, hence from the poorer classes of the population; and yet *v. Noorden* mentions that the course of Basedow's disease is to a high degree dependent on the fact whether the patient for a long time can be maintained until he has had time to regain his health. The material of the individual statistics is therefore very dissimilar. All statements on the side of the internists agree on the one point that in mild forms of Basedow's disease, recovery as a rule, as far as patients can spare themselves for a sufficient time (*v. Noorden*, *Oppenheim*, *Přibram*, *Chvostek*, *Mackenzie*, *Murray*, *Quine*, and *many others*). Special statements as to the curability of severe cases are not at hand. The statements as to curability are concerned only with the slight and severe forms together. I mention *A. Kocher's* statistics (internal cases) 18 per cent., *Syllaba's* 26 per cent., *Stern's* (of 19 cases, 9 almost cured), *Mackenzie's* 50 per cent. (very good result), *Quine's* 60–70 per cent., *Klemm's* 25 recoveries among 32 cases. Just as difficult is any idea as to the mortality (death from Basedow's disease itself, not from intercurrent affections). *Sattler* has collected the literature that is not too one-sided, and arrives at 11 per cent., *Kocher* states 22 per cent., *Leischer* and *Marburg*, 12–25 per cent., *Mackenzie* estimates the mortality in the acute cases as at 30 per cent., in cases in which icterus develops, the prognosis is extremely grave. Between these two extremes—recovery and death—lie the chronic and more or less improved cases, concerning the relationship of which to each other the figures again vary widely. Thus *Kocher* states 33 per cent. uncured, 27 per cent. improved; *Syllaba* 36 per cent. improved, *Stern*, of 19 cases of classic morbus Basedowi, 6 with slight improvement, 3 uncured. *Stern* mentions that the improvement may set in even after years. *Stern's* work is of great practical importance in so far as it shows that cases on a degenerative-neuropathic basis progress to full height, rarely die of Basedow's disease itself, and on the contrary, very rarely recover entirely.

In spite of the quantity of the material, its dissimilarity, as previously mentioned gives no certain result, at least not until according to *v. Noorden's* proposition there are separate statistics as to the disease in the well-to-do and the poor classes. Before I go into the question of internal treatment I would like to make a few remarks as to the results of *operation*. Concerning the method of operation, it should be mentioned that the ligation of arteries of the thyroid gland has to-day for the most part been discarded, because unsafe, and that mostly enucleation methods are practised, and sometimes excision and ligation are combined. The resection of the sympathetic, introduced by *Jaboulay*, practised especially by *Jonnescu* and by *Abadie*, has found but little vogue. Lately *Bérard* has stated that among 40 operations, there were 8 complete cures, 5 died at operation, 16 retained a small goiter, 5 were improved, and 5 remained uninfluenced. The latest statistics of *Kocher* include 376 own cases, of which 76 per cent. were cured (in one-fourth of these the exophthalmus was retained). The mortality was 3.9 per cent., the rest were improved or not cured; one-third of these cases were operated on more than once before the desired result was obtained. *Leischner* and *Marburg* report 45 cases (without compression symptoms) from *v. Eiselberg's* clinic, of which there were 6 cases of death (3 of the first 4 cases operated on died), 18 cured, 8 improved. *Mayo* has 4.75 per cent. mortality in 405 cases and 70 per cent. cures; *Schultze* (*Riedel*) reports among 50 cases 72 per cent. cured, 12 per cent. improved, 2 per cent. poor results, 12 per cent. deaths. *Landström* reports among 38 cases 52.6 per cent. cured, 18.4 per cent. improvement, 29 per cent. poor result, among which 5.5 per cent. death. I shall not enter into the older compilations, they are less valuable, as the methods of operation have improved since their time and also the indications for operation have changed somewhat.

If we consider that among the cases operated on just the mild cases seem to be rare from the better situated classes, that therefore the surgical statistics contain the especially severe cases, there is no doubt that all the surgical treatment in general surpasses the medical. To this should be added that after the operation the tachycardia usually diminishes; in a relatively short time, the body weight rapidly increases, even without hospital care, and working capability is rapidly attained. The difficult point of the question to-day is concerned with the *indications for operation.* Mild cases among the better situated classes should indeed not be recommended operation, nor should the chronic formes frustes on a degenerative-neuropathic basis (*Stern's* Basedowoid). Also *Kocher* points out that the results in these cases are less satisfactory. Operation is indicated in cases with compression symptoms. In the cases of pure Basedow's the social status should be decisive, because, as already mentioned, without doubt, operation leads more rapidly and certainly to working capability. A certain risk is always associated with operation, especially if a status thymico-lymphaticus is present. According to the statistics of *Capelle*, already mentioned, nearly 100 per cent. of the cases of Basedow's disease that died at operation had a hyperplastic thymus. *Hotz* therefore proposed to avoid operation if the X-ray transillumination shows a shadow. The demonstration of an enlarged thymus gland by means of the Röntgen procedure is however very uncertain. *Kostlivý* believes that the operation is especially dangerous in the cases without mononucleosis. This does not however meet with my view, because mononucleosis in the one and the same case may vary greatly (see previously). All these questions have not as yet been worked out fully.

Another question is as to whether one should operate early, or should await the results of internal therapy. A long period of awaiting is at all events unsuitable if the cardiac manifestations are well pronounced, as operation represents so much the less result the broader the cardiac dilatation and the more advanced the degenerative alterations of the cardiac muscle and of the other organs. On the other hand *Kocher* recommends a medical pretreatment as preferable, as far as no indicatio vitalis does not make an immediate operation necessary.

Of late a lively discussion has arisen concerning the reliability or the value of the irradiation of the thyroid gland with the X-rays. This was discovered by *Beck*, first used in Germany by *Görl*, and is warmly recommended in Vienna by *Holzknecht* and *G. Schwarz*. *Schwarz* has reported 40 cases in which after the irradiation the nervous symptoms always disappeared, and the tachycardia almost always; in two-thirds of the cases there were gains in weight, in about half the cases the exophthalmus retrogressed; only in one-third was the struma decreased in size. Also the cases that *Holzknecht* later reported showed a similar good result. *v. Eiselsberg* points out, however, that in three of the cases that had been treated with X-rays and that he operated on later, he found adhesions of the thyroid gland to the neighboring parts; on account of this the operation was essentially more difficult. Also *Hochenegg* reports three similar cases. It does not seem to me a priori that such adhesions are to be referred exclusively to the X-ray therapy. *Kocher* mentions especially that the operations of Basedow's strumas are made especially difficult through an especial density of the peristrumal connective tissues, through adherence of the external goiter capsule to the struma, in short through alterations that are similar to those of a chronic inflammation and are often found in strumas after a long treatment with iodine salve; on the other hand is it to be expected that there are tissue reactions to X-ray illumination that especially favor the development of such adhesions and that the fragility of the blood-vessels constitute a danger. In the discussion that followed *Holzknecht's* presentation in the Wiener Gesellschaft für Arzte [Vienna Association of Physicians], *v. Noorden* and *v. Strümpell* assumed an expectant attitude with regard to X-ray therapy, while *v. Wagner* and *Chvostek* condemned it. In a number of cases that I published from the first medical clinic since that time I have seen a right good result as the consequence of X-ray therapy.

I quote the following example: In one case the spontaneous glycosuria disappeared from the day of the first irradiation, in another case the weight curve, which in spite of week-long hospital treatment had continually sunk, began to rise only a few days after the first irradiation, the diarrheas disappeared, and after a few weeks the patient could again resume his studies as technician.

As far as the *internal treatment* of Basedow's disease is concerned, it must be sorrowfully said that all attempts to find a specific method of treatment have up to the present not led to certain results. *Ballet* and *Eniquez* first used for therapeutic purposes the serum of thyroidectomized animals, *Bunghart* and *Blumenthal* the serum of myxedema patients, *Sorgo* the meat of thyroidless herbivorous animals. *Möbius* used the serum of thyroidless animals (antithyroidin, *Merck's* preparation) or thyroidectin (*Parke, Davis, & Co.*), *Lanz* used the milk of thyroidless animals (Rodagen-milk powder of thyroidless goats, milk sugar). *Lépine* obtained an "immune serum" from the feeding of thyroidin to goats. Finally should be mentioned the thyrotoxic serum of *Beebe*. *v. Mikulicz* recommended the feeding of thymus substances. All these therapeutic propositions were for the most part greeted in the beginning with enthusiasm, but improvement was seen only in the light cases, in which the amelioration could not be attended with certainty by the means employed. In recent years too have the statements as to favorable results become always sparser. The scepsis is the more justified for the reason that all authors who have investigated the influence of thymus, rodagen, or antithyroidin serum on the metabolism have been able to elicit only negative results (*Magnus-Levy, Stüve, Salomon*). *A. Kocher* recommends neutral sodium phosphate (up to 6 gm. per day) which should prevent the dissemination of the iodine-containing substance from the thyroid gland. Views do not agree as to the value of this means of treatment. Otherwise medical treatment seems to fail almost always. All authors are, for example, of the opinion that digitalis rather aggravates the cardiac conditions. Also the diarrheas and vomiting are but little influenced by drugs.

*v. Müller* and *Saxl* proceeding from the experimental elicitation of *Loeb*, and of *Fröhlich* and *Chiari* that calcium exercises a dampening influence on certain conditions of irritation of the nervous system, have used in Basedow's disease intramuscular injections of calcium chloride gelatine (5–7 cc. of *Merck's* preparation "Kalzine"). They found in the typical cases mostly an essential improvement, while the treatment usually seems to fail in the case of an heredito-neuropathic basis.

The *dietetic physical* treatment remains to-day always in the central place of internal therapy. Most important is rest, in the severest cases rest in bed and the avoidance of every excitement, combined with the dietetic treatment; beneficial is the action of slight hydrotherapeutic procedures, such as were first recommended by *Winternitz*, eventually slight *galvanization* and *faradization of the sympathetic*, especially in strumas rich in blood-vessels, and the air of heights (600–1000 m.). Now a few words as to dietetic treatment. In the first place this must tend to prevent loss of weight and to enable gain in weight. As in Basedow's disease there exists an increased exchange, it was believed that this could be made up by an abundance of albuminous food. On the basis of our own investigations we were however compelled to accept the idea that administration of albumin increases the secretion of the thyroid gland. With this stands in harmony the fact that on administration of meat in experiments, we can make the thyroid gland extremely poor in iodine, thus bringing the stored secretion into the circulation on account of the greater need. I refer once more to the experiments of *Rudinger* carried out on the basis of these convictions, which showed that on almost albumin-free diet, very rich, however, in carbohydrates, we can depress the increased exchange to the normal. When therefore we administer abundant nitrogen-free energy carriers, we do not have to fear a loss of albumin. From such a diet should be expected not only a favorable influencing of the body weight, but also a certain mitigating influence on the hypersecretion of the thyroid gland; to which must be added that such a diet oppresses the least the gastrointestinal tract. As important as must be our endeavors to increase the body weight in Basedow's, not the less important is overfeeding to be warned against (*v. Noorden*), as the improvement of the cardiac activity does not keep pace with the increase of weight, and cases are known in which the increased demands on the heart, in consequence of the increase of weight, led to a sudden collapse.

## (b) Athyrosis or Hypothyrosis

**Historical.**—The first experiments as to the influence of extirpation of the thyroid gland on the animal organism originated with *Schiff*. To about the same time belong also the first clinical descriptions of myxedema on the part of *Gull*, *Ord*, and *Charcot*. *Gull*, in 1873, described five cases of "A Cretinoid State supervening in Adult Life in Women." *Ord*, in 1878, was the first to designate such cases as "myxedema." *Charcot*, in 1879, called the attention of the French to this clinical picture, terming it "cachexie pachydermique." The demonstration of the connection of this disease with the absence of thyroid function was furnished in 1882 and 1883, by *Th. Kocher* and *Reverdin*. In the period that followed this, thought was rendered confused by the fact that the symptoms following upon the removal of the parathyroids together with the thyroid were attributed to the absence of the thyroid. Investigation distinguished between acute and chronic cachexia thyreopriva. Only at the end of the nineteenth century did the clinical pictures of athyrosis assume stabile forms, through the detachment of the symptoms due to the absence of the parathyroids (*Gley*, *Vasale and Generali*, *Erdheim*, *Pineles*, *Biedl*). About this time, too, *Hertoghe* called attention to the mitigated forms of athyrosis. To-day one of the hardest problems is the relation of myxedema to cretinic degeneration. Although the fact that congenital absence of the thyroid as well as a severe disease of this organ in early life (infantile myxedema) had been established by animal experimentation and the recognition of the significance of thyroaplasia by *Pineles* in 1902, the careful analysis of the clinical manifestations between sporadic and endemic cretinism permit a recognition of far-reaching differences. Among these is the fact that in the first condition thyroid therapy is always successful, in the latter it sometimes fails. While we must ascribe certain of the important symptoms of endemic cretinism to thyroid insufficiency, many facts speak for the separate position of this illness.

I shall first describe those clinical pictures that develop through the failure of the thyroid-gland function in the fully developed organism because here the relations may be supervised so more readily.

## 1. Myxœdema Adultorum or Cachexia Thyreopriva Adultorum

**Definition.**—*This condition, resulting from the absence or insufficiency of the function of the thyroid gland in the adult organism, is characterized by the diminution of all vital processes and by certain trophic manifestations. The diminution affects the vegetative functions as well as the psychic life. There is found slowing of the entire metabolism and diminution of the excitability of the whole vegetative nervous system. The trophic disturbances affect especially the ectodermal tissues, skin, hair, nails, and teeth, although almost all organs may show regressive metamorphoses, especially the vascular system, which tends to be the seat of a premature arteriosclerosis.*

**Occurrence.**—Spontaneous myxedema of adults is a rare disease that is found somewhat more commonly in England and Holland [than on the continent]. In goiter districts typical myxedema seems to be relatively rare. Hereditary and familial occurrence is described by some authors (*MacIllwaine*, *Ewald*, *et al.*).

**Symptomatology.**—I begin with the description of the *alterations in the skin*, the most important of which has furnished for the disease its name myxedema. The myxedematous swelling may affect the skin of the entire body, but shows, however, a predilection for certain sites, the cheeks, lids, nose, supraclavicular fossæ, neck, backs of the hands and feet. The cheeks assume a yellowish color, but on account of small venectases are colored bluish-red in the middle. The nose and lips are also of this bluish-red color. On account of the swelling of the eyelids the palpebral fissures are much narrowed, and the deficient play of the features makes the expression of the face rigid and sleepy. In the supraclavicular fossæ develop thick cushions or pads that feel granular to palpation. The cushion-like swelling of the backs of the hands and feet make the extremities appear claw-like.

For the most part the swelling invades also the mucous membranes, the mucous membrane of the mouth assuming a whitish color, while the participation of the mucosa of the larynx leads to alterations of the voice; this becomes harsh and, according to *Magnus-Levy*, singing becomes impossible. The swelling of the uvula and the tonsils makes nasal breathing impossible; the patients breathe with open mouth and snore at night. The Eustachian tube and the tympanic cavity may also become involved by the swelling, causing a diminution in hearing-ability; and finally the female genitalia and the anus may become swollen. The tongue increases greatly in volume, so that it becomes visible between the rows of teeth, and shows impressions of the teeth. The increase in volume depends not only on the swelling of the lingual mucosa but also on alterations in the more deeply lying parts. Histological examination shows alterations of the muscle fibers and increase in connective tissue; the latter contains numerous nuclei and numerous new-formed capillary vessels. The tongue papillæ, too, become hypertrophic (*Maccone*).

The myxedematous skin looks like alabaster. It feels elastic, pressure with the finger evinces no pitting. It is dry and scales very much; the scales are mostly clayey. *Stevenson* and *Halliburton* ascribe the clay-like texture of the skin to the increased contents in mucin. They found the mucin-contents also increased in the salivary glands and tendons. *Halliburton* found in the blood and in the parotid of thyroprivic monkeys that the albuminous bodies precipitating to acetic acid amount to 3 per cent., while they were not demonstrable in the blood of normal monkeys. *Munk* also found mucin in the parotid secretion of a case of myxedema described by *Mendel*. But other authors found that the mucin-contents of the myxedematous skin was not increased, while *Bourneville* maintains that in the investigations just mentioned it is not certain that the substance dealt with was mucin, as in his investigations, no reducing substance was yielded by decomposition by means of acid. The microscopical investigation of the myxedematous skins show nuclear proliferation and new formation of connective-tissue fibrils, especially around the sweat-glands and sebaceous glands and around the hair follicles (English Myxedema Commission, *Virchow*). *Unna* found in skin of myxedemics substances that stained similarly to mucin, while *v. Wagner* and *Schlagenhaufer* found them in the skins of endemically cretinoid dogs and thyroprivic goats. A substance similar to mucin could also be observed (*Halliburton* and *Scholz*) in other organs, such as the kidney, the muscles, and the brain. That presence of this substance similar to mucin was missed by certain authors has perhaps its explanation in the fact that the accumulations of this substance are subject to much variation, and in cases of long standing they sometimes disappear. The skin then regains a flaccid lax texture and, in contradistinction to typical myxedematous skin, can be moved about on the underlying tissue.

Pigmentations of the skin occur relatively rarely.

The hair of the head and beard, the eyebrows, the axillary and pubic hairs become dry and brittle and often, in part, fall out. On the skull then develop large bald spots, that may lead to complete baldness. The nails become dry and cracked, the teeth become carious and fall out, and in the case to be described (Observation XII) the crowns of the teeth, in the course of a year since the myxedema had existed, had ground off entirely. The incisor teeth consisted of only short stumps provided with broad grinding surfaces.

The *circulation* is sluggish, the body temperature reduces, the patients are chilly, and can warm themselves with difficulty. The pulse is small and weak and slow—often only 50 to 60 beats a minute are observed. On body movements dyspnea readily occurs.

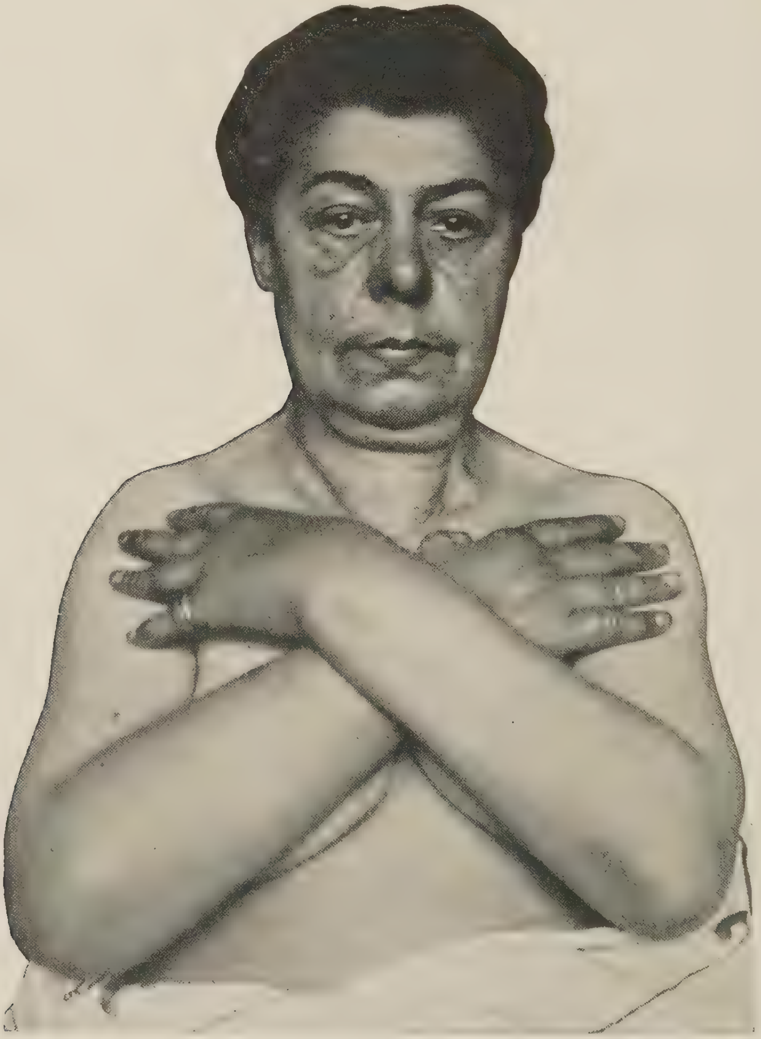

FIG. 10.—Postoperative myxedema.

*The excitability of the entire vegetative nervous system* and especially that of the nerves regulating the heart is diminished.

I here quote the clinical history of two myxedema patients in whom experiments were made as to the excitability of the vegetative nerves.

*Observation XI.*—Karoline K., sixty-four years, single. Entered clinic Nov., 1913. One uncle and one aunt on the mother's side suffered with struma. As a young girl the patient had a large neck, and of late years this has increased, producing difficulty in swallowing, difficulty in breathing, and indeed attacks of suffocation, on which account the patient was operated on in June, 1909. Nine days after the operation the patient was entirely well. In March, 1910, the hands and feet began to swell, the condition being taken for rheumatism. In the summer of 1910, myxedema was diagnosed, and an order given for thyroid tablets. Under this treatment the swellings retrogressed, but the patient became thin (loss of weight of 9 kg. in five weeks) and developed a marked tremor.

At present are seen swellings of the backs of the hands and feet, of the supraclavicular fossæ, and also of the face, especially in the vicinity of the eyes. The pulse is about 70. The skin is dry to the touch.

0.01 gm. pilocarpine subcutaneously; after one-half hour slight flow of saliva, no sweat.

100 gm. grape-sugar, no dextrose in the urine.

150 gm. grape-sugar, no dextrose in the urine.

Leucocytes, 6200, of which:

Polymorphonuclear neutrophiles, 62.6 per cent.

Eosinophiles, 5 per cent.

Lymphocytes and large mononuclears, 32.4 per cent.

After the instillation of homatropine into the eye, mydriasis occurs after about forty-eight hours.

A fully normal sella turcica to Röntgen examination.

In addition to the myxedematous manifestations are present slight signs of a primary chronic articular rheumatism (dry form).

Moderate constipation.

*Observation XII.*—Schw., F., thirty-eight years, entered September, 1910. First menstruated at twelve years of age, always regular, abundant flow. Two labors; since the last (eight years ago) which was followed by a hemorrhage, the menses have ceased. Since this time very poor appetite, patient always constipated. For one year the hands and feet often seem as if asleep, sensation of cold, formication in hands and feet. Speech has become slower. Often vertigo. Status: Skin pale, thickened and dry to the touch, hands cool, hairs thinned out and dry. Teeth small and loose, the chewing surfaces much worn down, so that the teeth are reduced to about one-half their length. In the axillæ and on the pubis the hairs are entirely absent. The facial expression is slightly catatonic, both lobes of the thyroid are palpable, internal genitalia atrophic, blood-pressure very low (between 60 and 70, *Gärtner*). 0.001 gm.[1] adrenalin subcutaneously; no glycosuria, no increase in blood-pressure.

100 gm. dextrose by mouth and at the same time 0.002 gm.[1] adrenalin subcutaneously; no glycosuria.

0.01 gm. pilocarpine; no salivation, sweating very slight. Slight increase in blood-pressure.

Erythrocytes, 3,500,000.

Hemoglobin, 70 per cent.

Leucocytes 7000, of which:

Polymorphonuclear neutrophile, 52 per cent.

Lymphocytes and large mononuclears, 42 per cent.

Eosinophiles, 6 per cent.

After the instillation of homatropine, mydriasis occurs after about thirty-six hours.

From the middle of October, thyroid tablets. At the beginning of November swelling of the face has disappeared, the skin about the eyes and on the clavicles very loose, facial expression very much livelier, hands now warm and less cyanotic.

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[1] German edition states mg. [= milligram]; evidently gm. is intended.—*Editor.*

A diminution in the excitability of the vegetative nervous system is demonstrated also by the experimental investigations in thyroidless animals. *v. Cyon* found a diminution of the excitability to electrical stimulation of the vagi nerves in such animals. The hyperexcitability of the accelerator nerves that he asserted to be present could not be confirmed. It is far more likely that the excitability of the sympathetic nerves is diminished. For this view speaks the failure of the glycosuric action of adrenalin in thyroidectomized animals and in myxedema patients. As regards the diminution of the pressor action of adrenalin we (*Eppinger, Falta,* and *Rudinger*) did not arrive at a certain result; while on the contrary, later investigations of *Bertelli* and *myself* show definite alterations in the reaction of the vascular system of thyroidless dogs against adrenalin.

As I regard the experiments important, I shall quote them in extenso.

15 kg. dog, ten days ago total extirpation of the thyroid gland with avoidance of the parathyroids. Electrical excitability remains unaltered.

| | Erythrocytes | Hemoglobin | Specific gravity |
|---|---|---|---|
| Before the injection | 4,900,000 | 45 per cent. | 1054 |
| 5 hours after the infusion of 3.69 mg. adrenalin | 4,100,000 | 45 per cent. | 1050 |
| 24 hours after this | 3,936,000 | 45 per cent. | 1051 |

Dog, 16 kg., total extirpation of the thyroid six weeks ago. Electrical excitability remains unaltered.

| | Erythrocytes | Hemoglobin | Specific gravity |
|---|---|---|---|
| Before the injection | 5,056,000 | 60 per cent. | 1050 |
| 1½ hours after infusion of 3.69 mg. | 5,932,000 | 65 per cent. | 1055 |
| 5 hours after | 5,680,000 | 63 per cent. | 1055 |
| 72 hours after | 5,016,000 | 55 per cent. | 1052 |

According to investigations of *Bertelli*, *Schweiger*, and *myself*, the erythrocyte count in *normal* dogs after the injection of adrenalin increases extraordinarily rapidly; after ten minutes it may reach 40 per cent., after five hours 70 per cent. In an experiment in which 4.36 mg. adrenalin was injected, it reached 100 per cent. after twenty-four hours; in another experiment after 3.69 mg. the hyperglobulia was indeed distinct, but had already begun markedly to decline. Although of course there occurred individual differences in the intensity and duration of the reaction, there was to be observed in all normal dogs a distinct rise. The hemoglobin contents showed a very much less increase. The specific gravity regularly showed a slight increase.

While, then, normal animals show after injection of adrenalin a high-grade hyperglobulia, in the production of which there is surely concerned, in addition to alterations in the permeability of the endothelium of the blood-vessels, also the pressing out of plasma on account of the long-continued contracted condition of the vessels, this manifestation was absolutely lacking or was essentially weaker in the thyroidless dogs. In this respect, individuals without thyroids show similarity to individuals with cachexia, who, as is known, do not react with hyperglobulia to the use of the lung suction-mask, or to sudden transference to great heights.

The autonomous nerves too show a diminution of their tonus and their excitability. *v. Cyon* observed, as already mentioned, a diminution of the electrical excitability of the vagi. The miotic action of pilocarpine in thyroidless dogs lasts for a shorter time (*Eppinger, Falta,* and *Rudinger*). The observations of *Asher* have already shown that in dogs with thyroid insufficiency the mydriatic action of atropine lasts for an abnormally long time. Hence the autonomous nerves are more readily paralyzed than under normal relations. Also in blood-pressure investigations on thyroidless dogs *Rudinger* and *I* observed that ruling out of the vagi through atropine lasts extraordinarily long. Finally, in some cases of myxedema I could establish an abnormally long mydriatic action on the instillation of homatropine into the eye (confer the analogous experiments in sporadic cretinism). *Fleischmann* observed that the blood of normal animals destroys the activity of added atropine more rapidly than the blood of strumous animals.

The previously mentioned alteration in the reaction of the vascular endothelium to adrenalin depends perhaps on the disturbances in nutrition, and these could be the cause of the premature arteriosclerosis of thyroidless animals, such as *Eiselsberg, Pick, Pineles,* and *others* have described. Also in myxedema patients do we frequently find striking grades of arteriosclerosis and depositions of lime salts, the latter even also in other organs such as the kidney, liver, etc. (*Abrikosoff*). Finally also in thyroaplasia has high-grade atheroma been found in the aorta and other vascular territories (*Bourneville, Maresch, Machand, Heyn* and *others*). *The occurrence of arteriosclerotic alterations* in thyroid gland insufficiency has been brought forward as the explanation of the senile degeneration. *Horsley* first pointed out that the thyroid gland in old age becomes atrophic, *Vermehren* compares old age with a chronic myxedema, while in more recent times *Lorand* has elaborated on this view. In opposition to this it has already been shown by *Ewald* that in marasmus senilis there is initiated not only an atrophy of the thyroid (and the other ductless glands) but also a degenerative atrophy of the other organs, especially the gastrointestinal tract. In any case at least we should be warned against an uncritical use of thyroid medication in old age (*v. Noorden*).

The diminution of the tonus or the excitability of the vegetative nerves is spoken for also by the *failure of the sweat secretion* in myxedema patients. The secretion of sweat may fail entirely even when there exists high external temperature or on bodily movements. *Mann* already observed that in myxedemics infusion of jaborandi did not bring about secretion of sweat. I, also, in the above-mentioned cases, observed after pilocarpine injection only slight salivation and no or only minimal sweating. Also in myxedema there is diminution of the function of the sebaceous glands (deficient oiling of the skin and hair). I have not found in the literature statements as to the secretion of gastric juice or pancreatic juice.

To a slight tonus of the autonomous nerves points the high-grade atony of the intestines that is the cause of the well-known obstipation of myxedema patients. Defecation in well-developed cases, if purgatives be not employed, may not occur for two or three weeks.

Almost constantly do alterations of the **psychic functions** accompany myxedema. The English Myxedema Commission found the apathy characteristic of myxedema absent in only three of one hundred and nine cases. This may develop relatively early, and in the light cases may consist in a sluggishness only of the previously mentally and bodily active patients, in a retardation of the psychic functions, in an inability to form rapid conclusions and in a slowing and monotony of the speech. According to *Magnus-Levy*, in light cases the "capability of reacting to strong stimuli" is for the most part not lost. In more well-developed cases there is a complete dullness, the patients brood, and there exists marked desire for sleep. The speech may be markedly slowed "als ob die Sprachwerkzeuge eingefroren wären" [as if the speech-mechanism were frozen in] (*Meltzer*). *Charcot* compares such patients to hibernating animals. Also in such individuals does the intellect tend to suffer, the memory, especially that for recent occurrences, becomes lost.

In such high-grade cases there are rarely lacking, in addition to this decided apathy, signs of a more deeply seated mental disturbance. Already at the beginning of the myxedematous disease or in the formes frustes are hallucinations commonly present, concerning which, as *Murray* says, the patient does not willingly speak.

The English Myxedema Commission found among the myxedema patients investigated by them illusions 18 times, hallucinations 16 times, and a frank psychosis 16 times. The psychoses belong to various types, although the melancholoid conditions predominate; and may of course consist only of a combination with myxedema. Very commonly, however, they stand in an intimate relation with myxedema in this respect—that through the myxedema a previously existing predisposition becomes manifest. In these cases the symptoms of the psychosis develop simultaneously with those of the myxedema and vanish after thyroid therapy has been instituted, to reappear again when the therapy is discontinued. Such a case has been described by *Pilcz*. In many cases, especially at the beginning, the inhibition is suddenly interrupted, and the condition may transitorily go as far as excitation.

*Horsley* distinguished between a neurotic stage that occurs at first, and a myxedematous or cretinoid stage, although this distinction may have been influenced by the tetanoid manifestations after thyroid gland extirpation which at that time were ascribed to the absence of the thyroid.

Other coarse disturbances that are routinely looked for on the investigation of the *nervous status* are not as a rule found. The reflexes are for the most part normal, only rarely are diminution or increase of these stated. Not rarely the patients complain of paresthesias and of rheumatic pains. The test for sensibility for the most part normal, at the most it has been stated the slowing of conduction is present, although this finding is by no means constant. It has been recognized that testing of sensation is hard to carry out in heavily apathetic patients. The same holds good for tests of the smell, taste, and hearing. Most common of these is disturbances of hearing. The English Commission found them in almost half of the cases investigated by them. The cause for them has not as yet been certainly ascertained. *Wagner v. Jauregg* assumes that they are produced by myxedematous swelling of the mucous membrane of the tympanic cavity and the tube. It is, however, often very hard to determine what part the lessened power of apprehension of the central apparatus and the lacking apperception plays in this; in any case it is significant that the disturbances of hearing react promptly to thyroid medication.

The conductivity of the skin for the electric current is diminished on account of the high degree of dryness. It has further been stated that in many cases there is diminution of the electrical excitability of the nerves and muscles. In one case *Erb* found it normal. *Rudinger* and *myself* found an appreciable diminution of the galvanic excitability of the nerves in thyroidless dogs. The investigation was conducted three months to one and one-half years after extirpation of the thyroid. Instead of the normal value of 1.2–1.5 milliamperes we needed 2–3 milliamperes in order to produce (test of the sciatic nerve) a cathodal closing contraction. In one case of myxedema *Erb* found a slow twitching of the muscle to mechanical irritation. The motor processes, too, are conducted slowly. The movements are extremely slowed, the gait heavy, slow, and slightly staggering. One of the early symptoms is a quickly appearing tiring, only on the longer duration of the disease is the motor power diminished. The cause of all alterations in function of the central and vegetative nervous system lies in nutritive disturbances. *Walter*, *Marinesco* and *Minea* found in thyroidless dogs a slowing of degeneration and regeneration of the nerves.

There is not much known concerning alterations in the **osseous system** in myxedema. *Stubenrauch* describes in a case symmetrical changes of the bones and joints of the feet. Both first interphalangeal joints were destroyed, the middle and end phalanges showed in part abnormal transparence and in certain places direct loss of substance. We should be cautious about bringing such alterations into relationship with myxedema and must first look for more observations of the same sort.

The examination of the **blood** shows decrease of the red cells, and especially of the hemoglobin, the latter to 60 per cent. or even 40 per cent.; also decrease in the dry residue and increased coagulability (*Bultschenko* and *Drinkmann*, *Kottman*). The leucocytic formula is altered, consisting in mononucleosis and mostly hypereosinophilia (*Bence* and *Engel*, and the *author*).

In many cases are observed erythroblasts and slight poikilocytosis, in others also *Türk's* irritation forms and myeloblasts. In one of the cases herein quoted were found indeed isolated myeloblasts. Similar blood changes are also found in thyroprivic animals (*v. Eiselsberg*, *Zitschmann*, *Kishi*, *Esser*, *Bertilli's* investigations on our own dogs). The anemia quickly ameliorates on the administration of thyroid gland substance, and there occurs a "paradoxical" reaction of the leucocytes, *i.e.*, the leucocytic formula approaches the normal, while in healthy individuals it is known that thyroidin produces mononucleosis (*Falta*, *Newburgh*, and *Nobel*). More recent investigations of *Fonio* agree with these; interruption of the thyroid-gland therapy for the most part brings about a recurrence of the mononucleosis (*von Korczynski*), while the poverty in hemoglobin also is essentially ameliorated by the thyroid-gland therapy.

The **metabolism** of myxedemics is reduced to a marked degree. We are indebted to *Magnus-Levy* for the discovery of this. He found a reduction of the fundamental exchange to 58 per cent. Treatment with thyroidin brings the fundamental exchange to normal or supernormal figures.

If the thyroid gland therapy be interrupted, the amount of oxygen consumed gradually sinks as the clinical symptoms recur. Also the twenty-four-hour exchange is reduced, that is, myxedemics maintain an equilibrium with a much less amount of calories and take on fat more readily than does the normal individual.

Sometimes accumulations of fat are found at entirely abnormal sites. Thus *Abrikosoff* found in a fifty-two-year myxedematous woman accumulations of fat in the lingual mucous membrane and in the submucosa of the intestine. If myxedemics are nourished abundantly, the twenty-four-hour exchange does not necessarily have to be below normal, and thyroidin administration will then produce an enormous increase in the caloric production. *Steyrer* found in his case an increase of 83 per cent. (investigation in *Voit-Pettenkofer's* apparatus). Especially fat is concerned, while the number of calories from albumin is rather less than normal. Also the albumin exchange lies low, the albumin requirements are light, and there may be an addition of albumin to the body. The relations in investigations as to the hunger albuminous exchange are very clear. In thyroidless dogs we found this distinctly reduced.

The time consumed in the albumin destruction in thyroidless dogs is, according to the investigations of *Pari*, not altered. Administration of thyroidin leads, in the wake of the consumption of myxedematous tissue, at first to a significant increase of the nitrogen excretion, this giving place to normal relations. The relations of the salt metabolism in myxedemics is not as yet fully explained; it is to be expected that the need for salt is slighter and that less calcium is cast off in the feces, as the administration of thyroidin allows more calcium to pass out through the intestine. The amounts of urine in myxedemics as a rule are very small. Often slight albuminuria is found, that may probably be attributed to nutritive disturbances in the kidneys.

The assimilation limits for grape-sugar, in myxedemics, is raised (*Hirschl*, *Knöpfelmacher*). *Hirschl* found no glycosuria even after the administration of 500 gm. of dextrose. Also in thyroprivic dogs the administration of sugar (up to 200 gm.) does not lead to glycosuria, although in dogs the assimilation limits lie relatively low. In thyroprivic dogs the glycosuric action of *adrenalin is reduced* (*Eppinger*, *Falta*, and *Rudinger*, *Pick* and *Pineles*).[1] Myxedemics show the same relation.

In a case of *Herz's* the administration of dextrose with the simultaneous injection of adrenalin did not lead to glycosuria. I found the same thing in the case described above (Observation XII) (100 gm. dextrose together with the simultaneous administration of 2 mg. adrenalin subcutaneously). After a long-continued thyroidin medication the relations become normal again. In the case of *Herz*, after successful thyroidin treatment, traces of sugar appeared in the urine after only 100 gm. of dextrose. Adrenalin now again produced glycosuria.

The inclination to glycosuria can also remain after the withdrawal of thyroidin treatment. As example I quote the following case:

*Observation XIII.*—Rosa L. Entered the clinic June, 1895, then fifty-two years old. From the history taken at the time, three confinements, first menstruation at the age of fifteen years. After the confinement the menses were irregular and sparse, and ceased three years ago. Then abdominal pains, jaundice, followed by a marked swelling of the neck that gradually retrogressed again. Since that time there has gradually developed, especially since the winter of this year, the following disease-condition: great languor, rapid fatigability, rheumatoid pain, swelling of the upper and lower extremities, the face, the eyelids, hoarseness of the voice, constipation and distention of the abdomen, bloated condition of the face, swelling of the lips, tongue, and eyelids. The swelling of the tongue and lips is so intense that it hinders eating. There are subjective sensations of cold, especially on the back. Often severe headaches, sensation of vacancy in the head, and feeling of anxiety.

From the status: Skin of the extremities and on the abdomen thick, cool, and cyanotic.

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[1] The alimentary glycosuria that is observed in thyroparathyroprivic dogs (*Falckenberg*, *R. Hirsch*) is to be ascribed to the absence of the function of the parathyroids. (Confer also *Falta* and *Rudinger*.)

There are present on the upper and lower extremities, and in part on the trunk, signs of ichthyosis. The face, and especially the eyelids, are swollen out, so that the skin in the vicinity of the eyes is markedly wrinkled. The facial expression is exquisitely sleepy, the forehead transversely wrinkled so that an astonished expression is produced; the hairs are dry and very much thinned out (of late years especially have fallen out). Face somewhat markedly pigmented, lips protruded in a somewhat snout-like manner, the teeth for the most part are missing or are loose. In both supraclavicular fossæ slight cushion formation. On the left the lateral lobe of the thyroid somewhat palpable. Great drowsiness, and slowness of all movements. Speech very slow. Weakness of memory. Gait awkward, dragging. Great fatigability. The patient was given at times thyroidin tablets, which however produced cardiac palpitations and turned the constipation into diarrhea. However, under this treatment the swellings disappeared very rapidly. In 1897 she tried thyroidin tablets, without deleterious effects. She took them ordinarily for about fourteen days, during which time she lost weight rapidly, then she would discontinue them for about four weeks, until the pockets on the eyelids and the thickenings on the abdomen appeared again. In 1895 the patient was almost bald; later the hair grew again and at present she has a growth of hair about usual for a woman of her age. She perspires hardly at all. For two months she has again discontinued the thyroidin medication, and all the above-mentioned manifestations have recurred to an exaggerated degree. After 100 gm. of grape-sugar the patient shows a distinct although not very strong glycosuria; sharply delimited cyanosis of the cheeks.

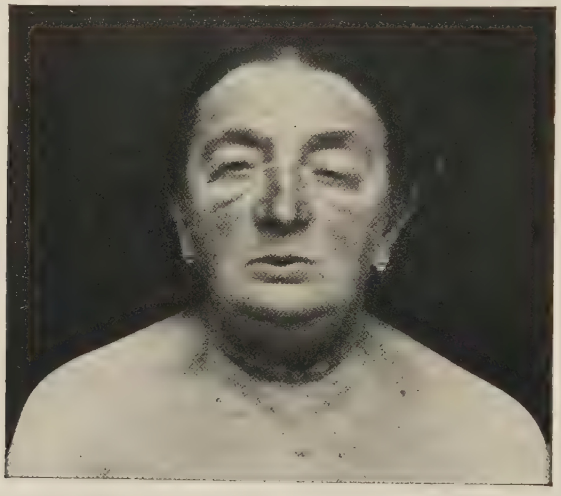

FIG. 11.—Case of myxedema with tendency to glycosuria.

There is indeed no doubt that since the year 1895 the patient has suffered from a typical myxedema. Perhaps at that time a thyroiditis appeared together with the jaundice, which gradually led to insufficiency of the thyroid gland. The combination with ichthyosis had been often described by French authors. From the beginning, the case showed no high tolerance for thyroidin, although there was already present a myodegeneratio cordis. I can readily appreciate that in such cases palpitations can occur even when the doses are not too high.

The observation that the alimentary glycosuria resulted positive, in spite of the two months' cessation of thyroidin medication, points to the fact that here, in addition to the thyroid gland, the pancreatic insular apparatus is also degenerated.

In this case I prescribed small doses of thyroidin, and at the same time hypophysis tablets, as I suspected a degeneration of the glandular portion of the hypophysis also. I need only mention the fact that this medication was borne for several months without calling forth the previous cardiac distresses, and that thereby the recurrence of the myxedema symptoms was prevented. The puffiness on the neck and face has disappeared, the scaling of the skin which has existed for eighteen years has disappeared, the skin has become smooth and elastic, the itching has ameliorated; only the brittleness of the nails has remained unaltered (communication by letter).

The explanation for the simultaneous existence of myxedema and an inclination to glycosuria that I sought in this case would serve also for any case that under thyroid therapy proceeded to spontaneous glycosuria (*Macfie Campbell*, *Bramwell*, *Ewald*, *Osler*, *et al.*), or that without thyroid therapy showed a tendency to glycosuria (*Garnier* and *Lebret*). Also combinations of myxedema and diabetes are observed, but indeed appear to be very rare. The case of *Apert* was that of sporadic cretinism with distinct myxedematous manifestations. In this case growth ceased only at the age of thirty-six years. Later diabetes appeared. I believe that it is intelligible that absence or insufficiency of the function of the thyroid leads to hyperfunction of the pancreatic insular apparatus only when this is capable of functionating. If the pancreas itself is diseased, diabetes may occur, even when the thyroid fails. This is shown by the experiments of *Eppinger*, *Rudinger*, and *myself* on the pancreatic diabetes of thyroidless dogs. If, however, myxedema is superadded to an already present glycosuria, the glycosuria tends to disappear. Thus *v. Noorden* reports fourteen cases of endogenous obesity, of whom seven formerly excreted slight quantities of sugar. With the development of the forme fruste of myxedema the sugar disappeared, and even a high tolerance for carbohydrates commenced. Only in one case did the glycosuria persist, in mild form, during the myxedema.

The diminution in the general metabolic processes in myxedema expresses itself also in *hypothermia;* this belongs to the commonest symptoms of the fully developed forms. The rectal temperature varies between 36° and 37° Celsius, and may even be below 36°. It stands in relationship with the sensations of cold complained of by the patients. Myxedemics feel comfortable only when the external temperature is high; their condition aggravates in the cold season of the year; it has even been stated that in summer time we may need to administer smaller doses of thyroid-gland substance in order to compensate for the deficiency, and must increase the dose in winter. Strong stimuli, as for example infectious diseases, may, however, also bring about hyperthermia as numerous examples in the literature bear witness.

In severe cases of myxedema there regularly develop disturbances in the *sphere of the genitalia*. Women develop irregularities of menstruation; either the menses cease or there occur profuse floodings. In the long-standing cases premature climacteric occurs and often a high degree of atrophy of the genital apparatus (*Landau, Szanto*). In two women with distinct cachexia strumipriva, *Langhans* found pronounced small-cystic degeneration of the ovaries. *Allen Starr, Kirk, Schotten* and after them many others have testified to the occurrence of menorrhagia. In men, libido is lost. Very instructive in this connection is a case of *Magnus-Levy*, in which a fifty-four-year-old man lost libido completely, and regained it after cure of his illness. *Herz* observed a similar case in which a forty-five-year-old man regained erections and ejaculations two weeks after the beginning of treatment. Treatment by thyroid gland also affects favorably the menstrual disturbances in women. These do not signify sterility, as there are known to be cases of myxedema in which occurred conception and normal pregnancy. It is shown also by animal experimentation (*Halsted*) that partial extirpation of the thyroid does not prevent normal carrying of young. In such cases the thyroids of the fetuses seemed to act compensatorily. In other words, *Halsted* observed in the new-born pups an enormous hypertrophy of this organ. The thyroids were about twenty times as large as in a normal new-born pup. In cases with a long-standing high-grade deficiency of thyroid function, there occurs atrophy of the ovaries. In this case the disturbance seems to be irreparable.

In cases of myxedema the *hypophysis* is commonly described as altered. *Boyce* and *Beadles* found enlargement of this organ, as did also *Ponfick* in a case. In a case of *Abrikosoff* the glandular portion of the hypophysis was enlarged, and indeed the chromophilic cell-columns were increased, the cells enlarged, their protoplasm showing colloid degeneration. *Comte* earlier observed a similar condition and considered the enlargement of the hypophysis as a compensatory hypertrophy. In other cases there has occurred a pronounced sclerotic degeneration of the glandular hypophysis (2nd case of *Ponfick*) or cystic degeneration (*Sainton* and *Rathery*, and *others*). In both the cases of myxedema above reported the sella turcica as shown by X-ray was normal.

An enlargement of the hypophysis after extirpation of the thyroid has been observed in animal experimentation. In grown animals *Bertelli* and *myself* (reports not published in detail) could not find anything similar after a one and one-half years' duration of the thyroprivic condition. I think that the findings described are overestimated as to their significance for the reciprocal action between thyroid gland and the glandular hypophysis. The vicarious action of the hypophysis for the thyroid gland, as *Comte* assumed, need not be considered in this connection. It is just as if in contracted kidney the liver acts vicariously for the kidney. In myxedema adultorum the hypophysis sustains mostly changes of a strumous character, or simultaneously with these, changes of a chronic inflammatory nature (as for example in the cases of *Ponfick, Sainton* and *Rathery, et al.*), such as we shall meet with again in the consideration of multiple ductless glandular sclerosis. Simultaneous disease of the thyroid gland and the glandular hypophysis (pathological correlation) is very rare. I shall deal with it in detail in the chapter on the hypophysis. Often in such cases thyroid gland medication causes a disappearance of only a portion of the cachectic symptoms. We shall deal later with the alterations in the hypophysis in infantile myxedema. The combination of myxedema with tetany is considered in the fourth chapter.

**Etiology and Course.**—We to-day possess a complete explanation of the etiology of myxedema operations. Total extirpation of the thyroid gland always leads to myxedema, which in very rare cases may be only slight and may heal spontaneously, this manifestation being due to the compensatory hypertrophy of accessory thyroids (cases of *Vollmann* and *Reverdin*). It is very much worthy of note that in cases of accessory struma of the base of the tongue, extirpation of the tongue struma led to myxedema. *Seldowitsch* and *Chamisso* have each reported such a case. After operations for struma, mitigated forms of myxedema operations often appear, forms that show, for example, only disturbances of growth, or only fat deposits, or only apathy. Among thirty-eight cases of cachexia strumipriva, *Kocher* saw the mitigated form only nine times; here recurrences of the goiters developed. If a thorough continual treatment with thyroidin be not instituted there is shortening of the thyroidectomized individual's life. Total thyroidectomies are to-day still performed only on malignant degenerations of the thyroid gland. Mitigated operative myxedema may also occur to-day where there is intense degeneration of the part left behind.

The pathologico-anatomical finding in the thyroid in so-called spontaneous myxedema is ordinarily sclerosis with destruction, or a high-grade goitrous degeneration. In many cases of spontaneous myxedema is found on the site of the thyroid only fat and connective tissue (*Abrikosoff*). Only in rare cases is the etiology of the inflammatory cirrhosis clear, as for example in *Kohler's* cases of syphilis and actinomycosis respectively of the thyroid, the first yielding to the effects of potassium iodide, the latter to operation. *v. Wagner* observed two cases of formes frustes in the eruptive stage of syphilis; in the later stages of syphilis infiltrates and gummata are present. Tuberculosis of the thyroid gland is relatively not very common. Also miliary tuberculosis has been observed. Primary tuberous tuberculosis seems to be very rare. In certain cases of multiple sclerosis of the ductless glands there is found in the thyroid, in addition to diffuse chronic processes, also, in some places, tuberculous foci. In most of the cases of spontaneous myxedema there were perhaps other infections than those stated. The territory has not as yet been explored bacteriologically. An index is furnished by those cases of myxedema that appear after cases of infectious diseases. Thus *Reinlinger* reports a case of an individual, twenty-two years old, who after a gastric fever (typhoid?) developed cachexia, myxedema of the skin, apathy, dementia, and falling out of the axillary and pubic hair. Thyroid therapy produced good results. *Marfan* saw myxedema develop after an acute articular rheumatism with angina. Sometimes, as previously mentioned, the hyperplasia of Basedow's disease goes over into atrophy. The investigations of *Roger* and *Garnier*, *de Quervain*, *Sarbach*, *Bayon*, and *others* have shown, however, that in severe infectious diseases there regularly develop in the thyroid processes that are inflammatory, and that in chronic intoxications cirrhotic processes frequently develop.

The reason that myxedema is commoner in women than in men should be sought in the fact that the normal sexual processes in women determine an important affection of the function of the thyroid, and that an exhaustion of this is produced the more easily by damages to the parenchyma due to common infections or intoxications. For this assumption speaks the fact that mitigated forms of hypothyrosis tend to become worse during pregnancy and that not rarely the myxedematous symptoms disappear at the sexual involution.

Finally, it should here be mentioned that sclerotic processes are found in the thyroid in numerous cases of scleroderma (*Singer*, *Hektoen*, *Roux*, *Leredde* and *Thomas*, and *others*). Eventually, in many cases of scleroderma are found also symptoms that remind one of myxedema (*Gresset*, *Osler*, and *others*). As scleroderma involves in sympathy the most diverse organs, we readily see that we should best regard the alterations in the thyroid as a partial phenomenon of the fundamental processes (see Chapter I).

**Differential diagnosis** is concerned first of all with nephritic edema. Slight presence of albumin [in the urine] may also occur in myxedema. We should especially consider the density of the swellings, the failure of hypertonia, and the presence of psychic alterations. Also, in myxedema, the swellings are often more distinct in the mornings than in the evenings.

Normal psychic relations also distinguish from myxedema, stabile erysipeloid edema, indurative syphilitic edema, and pachyderma; again, these do not react to administration of thyroidin. Thyroid medication may affect favorably scleroderma (stimulation of metabolism, *Ewald*); the same holds good of certain cases of lipomatosis dolorosa (*Dercum*). In many such cases alterations are found in the thyroid, in others in the hypophysis (see Chapter XIV).

The *incomplete forms* of myxedema are of difficult diagnosis. *Hertoghe* first drew attention to these, designating them chronic benign hypothyroidism. They are much commoner and more multiform in women. They often begin with chronic muscular pain, which may disturb sleep. Rachialgias are especially frequent, to which may be added great lassitude, especially in the morning hours, menstrual disturbances, menorrhagias or amenorrhea, sensation of cold, even shiverings, hoarseness of the voice, and especially often rather obstinate constipation. The picture becomes clearer when the hair begins to fall out, especially that over the occiput, and when apathy and depression are added. Sometimes many persons in the same family are found with the signs of chronic mitigated thyroid insufficiency. *Hertoghe* mentions that pronounced signs of myxedema in children first drew his attention to the signs mentioned in the mother, and then that treatment of the mother with thyroid substance brought about good results. *Gluzinski* remarks that such abortive forms of myxedema in women not rarely occur in the years just before the climacteric and retrogress when the climacteric has been completed. The last statement has also been mentioned by *Hertoghe. Kocher* and *Fr. Kraus* agree with *Hertoghe* concerning the frequency of such forms. *Kocher* mentions that not rarely manifestations of chronic rheumatism that are associated with pains, stiffness, and heaviness of the extremities depend upon a larval hypothyrosis. The diagnosis may also be made more difficult by the fact that distentions of the joints develop. *Parhan* and *Papiniam* have described a case of chronic rheumatism which they regarded as dysthyrogenic. *Rothschild* and *Levi* have tried thyroid therapy on a large group of cases of chronic articular rheumatism. There were twenty moderately severe and light cases among thirty-nine cases varying from twelve to fifteen years of age. Of these, eighteen were cured or essentially improved, while of the severe cases, two were cured and thirteen improved. One should be very careful about regarding these forms of articular rheumatism as thyrogenic, as it is not unlikely that good results may be brought about solely by the stimulation of the metabolism through the thyroid medication.

*Hertoghe* certainly goes too far when he brings myomata, retroflexion of the uterus, emphysema, congestion of the liver and gall-stone formation directly into relation with the thyroid gland insufficiency (*Kocher*, *Fr. Kraus*). That on the other hand we were justified in ascribing, in many cases, the above-cited manifold disturbances to a chronic light thyroid insufficiency speaks the fact, quite apart from therapeutic results, that *Kocher* not rarely saw such "thyroprivic equivalents" occur after strumectomy.

The diagnosis of such benign forms of thyroid-gland insufficiency can, as can readily be understood, present great difficulties, especially when only a few of the manifold symptoms are present, for instance, increased heaviness of the nasal breathing, hoarseness of the voice, or a slight degree of deafness. Especial attention is to be directed in these cases to the presence of pseudolipomata in the supraclavicular fossæ or to transverse folds in the forehead (*v. Wagner*). Often the diagnosis can only be made tentatively ex juvantibus.

An especial form of mitigated thyroid insufficiency is *thyrogenic obesity.* In contradistinction to so-called dietary obesity there are cases in which obesity develops in spite of slight supply of calories, and remains present when the supply of calories is so restricted that normal individuals of the same size, of the same weight, and under the same living conditions would rapidly lose in bodily weight under such conditions. The cause of endogenous obesity is of very diverse nature (see also Chapter VI, on the hypophysis, and the various forms of obesity, Chapter XIV). But it can hardly be doubted that one of these causes is a slight grade of thyroid insufficiency. The thyrogenous obesity may depend on inherited predisposition or may follow infectious diseases (*v. Noorden*). Also it may be preceded by a Basedow's disease. I refer to the cases of Basedow's disease in which the initial emaciation is followed by a progressive increase in weight. For the diagnosis of thyrogenous obesity, important also are other symptoms such as phlegma and constipation, especially if they have existed before the development of obesity. Such cases belong in the domain of thyroid treatment; restriction of calories in such cases can, especially in older persons, lead to a marked exhaustion and cardiac collapse, without lessening the amount of fat, while administration of thyroid gland reduces the body weight with amelioration of the general condition (*v. Noorden*).

The cause of the manifoldness of the hypothyroidal syndrome may be regarded, as in the hyperthyroidal syndrome, as constitutional differences of the affected individuals.

The course of myxedema in untreated cases may be progressive and give rise to a cachexia; mostly then intercurrent affections occur, and lead to death. Spontaneous improvement may also occur, not rarely with the development of a goiter, in rare cases with hypertrophy of the accessory thyroid glands.

The treatment of myxedema will be considered after the description of sporadic cretinism.

## 2. Sporadic Cretinism

**Definition.**—In the preceding section we drew disease pictures that originate in an organism already fully developed, when the thyroid becomes insufficient or loses its function entirely. When the disturbance in thyroid function develops in an organism as yet unfinished, there are in addition added to the phenomena described profound developmental disturbances that are the more intense the earlier the disturbance begins. The conception of sporadic cretinism as hypothyrosis or athyrosis of the youthful organism is decisively proved in the first place by the sad experiences that were sometimes met with at a time when the function of the thyroid were not known, in strumectomies on children, and in the second place by the fundamental researches on total extirpation of the thyroid in animals (of *Hofmeister* and of *v. Eiselsberg*). The thyroprivic animals of *v. Eiselberg* that were kept under the same conditions as the control animals showed, as against the control animals of the same brood, after a few weeks, a considerable remaining behind in size and in body weight. The disturbance in growth affected more the long bones than the trunk. The bones became coarse and showed decrease in solidity. After a longer time the bodily weight of the control animal often attained to three times that of the thyroprivic animal. In addition were found distention of the abdomen, anemia, atheromatous degenerations of the great vessels, atrophy of the genitalia, reduction in temperature, curving of the bones, trophic alterations of the hair, dryness of the skin, senile marasmus, and pronounced idiocy, in short the picture of idiotic dwarfism. The changes in human beings when the function of the thyroid becomes deficient in early life are entirely analogous. The lack of thyroid may be either congenital (*thyroaplasia* or *thyrohypoplasia*) or the same changes that cause myxedema of adults may affect the thyroid in early life (*spontaneous infantile myxedema*), or, as already mentioned, a surgical procedure may lead to thyroid insufficiency (*postoperative infantile myxedema*).

*Pineles*, who was the first to separate thyroaplasia from the entire group as an etiologically unitary form, wished to avoid the expression sporadic cretinism and to distinguish only between thyroaplasia and infantile myxedema. It seems to me, however, that this sharp distinction is not practicable. It is true that infantile myxedema makes its first appearance in the fifth or sixth year of life, while in thyroaplasia the exhibition of development begins gradually to manifest itself already in the first year of life. Infantile myxedema may, however, also develop at the earliest age. If the damage to the thyroid in these cases is a material damage, the intensity of the inhibition of development is the same as in thyroaplasia, and as the finding on palpation when negative is not decisive, so a certain differentiation between these two conditions is hardly attainable in vivo, especially if the individuals first undergo an exact physical examination at a later stage of life. I therefore wish to retain the name sporadic cretinism for the entire group. *Siegert* embraces all the cases of lack or deficiency of the thyroid gland in children, together with endemic cretinism, under the name myxidiotie [myxidiocy]. As I do not regard endemic and sporadic cretinism as entirely of similar nature, I cannot subscribe to this designation.

In his excellent work on thyroaplasia, *Pineles* collects from the older literature twelve cases in which the thyroid was absent microscopically at autopsy. Almost all the individuals affected died at an early age; in the fewer older individuals who had attained the age of puberty it seems that the demonstration of a complete aplasia of the thyroid was not certain, or the cases had been treated with thyroid tablets (*MacCallum* and *Fabyan*). Also *Thomas Erwin* remarks this. In the case of *Fletcher-Beach*, that concerned a fifteen-year-old girl, a certain intelligence had developed. She had learned to write and use figures, and had menstruated two or three times. The autopsy indeed showed absence of the thyroid gland, but as such a development is hardly possible with a complete thyroaplasia—the publication of this case occurs before the era of thyroid-gland therapy—it is possible that here accessory thyroids were present, which could not, however, fully compensate the deficiency. *Pineles* then cites seven works of a more recent date in which an exact microscopical examination failed to find any remnants of thyroid gland (*Kocher-Langhans, Muratov, Maresch, Peucker, Aschoff, Erdheim, Knöpfelmacher*). The case of *Maresch* was that of an eleven-year-old girl whose brothers and sisters were perfectly well; according to the statements of the parents, growth ceased almost entirely at one and a half years of age. At eleven years of age, the girl was 77 cm. tall, the skull had a circumference of 49 cm., the abdomen 53 cm., the great fontanelle measured 4¼ cm. by 1½ cm. The girl could not walk, could only sit, and could speak only a few syllables. The skin was myxedematous (also on microscopical examination), the hypophysis was of normal size, the thymus gland corresponded with the age. Pancreas and suprarenals were of normal size.

The contribution of *Maresch* was of fundamental importance, because *Maresch* established for the first time in his case the presence of the parathyroid glands. Also later investigators found the parathyroid glands intact. Only in a few cases was the simultaneous absence of parathyroid glands reported (*Quincke*, Case I, *Rocazet Cruchet*, two cases of *Siegert*). Here, however, no serial sections were made.

Very exactly studied are the cases of *Aschoff*, *Erdheim* and *Diederle*.

The case of *Aschoff* was that of a half-year-old child of 53-cm. length. The hypophysis was very much enlarged (0.5 gm.). *Aschoff* found at the root of the tongue a cystic tumor that he regarded as the remnant of the lingual duct. In addition, there was found at the site of the lateral thyroid lobe a half-pea-sized vesicle that he regarded as the remnant of the branchial pouch. The case of *Erdheim* was a thirteen-month-old child, the thirteenth child of healthy parents. High-grade constipation had been present (palpable fecal tumor). Here also was found the vesicle as in the case of *Aschoff;* microscopical examination showed that it consisted of an ectodermal formation, as to the origin of which from the fourth branchial pouch there could be no question, as *Erdheim* found the same cysts on this side in two cases of unilateral thyroaplasia, in which cysts on the normal side were absent.

Very recently have been added the cases of *Ungermann* (vicarious tongue-struma), *MacCallum* and *Fabyan* (cysts in the neighborhood of the superior parathyroids), and finally three cases of *Schilder*. In all cases exactly investigated up to the present these cysts have been found at the site of the lateral lobe of the thyroid. *Diederle* could also demonstrate in his case the absence of the rudiments of the superior thyroid arteries.

We are therefore justified in the assumption that in these cases an anomaly of formation is present that consists in an agenesis of the lateral rudiments of the thyroid. The vesicles found at their site consist in indifferent rests of the postbranchial bodies, in which under circumstances isolated thyroid follicles may be imbedded. At the root of the tongue are found at the site of the median rudiment of the thyroid gland analogous indifferent rests with traces of thyroid gland tissue, which not infrequently give occasion to tumor formation. The cases described affect children who have reached the eleventh year of life at most. The girls were far in the majority; they were all well developed at birth. Only in the second half of the first year of life did there gradually occur a standstill in the development. Under the numerous cases of sporadic cretinism described in the literature a large number certainly belong to thyroaplasia. *Diederle* counts among others also the two cases of *Kocher* and the known case of *Bourneville* (*Pacha de Bicêtre*). Also two cases of *Magnus-Levy* belong to this group. The above-mentioned case of *Bourneville* attained an age of thirty-six years. As I have said before, I would rather not take up the question whether pure cases of thyroaplasia can reach so old an age, especially if they have not been previously treated. In any case it is established that also in complete absence of the thyroid gland, life and a certain degree of development is possible.

**Symptomatology.**—I shall now describe the clinical picture of sporadic cretinism without regard to the etiology of special cases. We must in every respect consider that only those cases which show the fully developed clinical picture can belong to the thyroaplastic form, while in the incomplete forms only a relative insufficiency of the thyroid function must have begun later.

I would like to describe three cases of sporadic cretinism that *Herr Hofrat Wagner v. Janeregg* kindly allowed me to examine.

*Observation XIV.*—Margerete H., two and one-half years. Entered the psychiatric clinic (of *Wagner*) Nov. 4, 1909. Father has a goiter, avowedly from blowing the buglehorn. Otherwise no goiter in the family. Her mother's mother was insane. Parents have never been away from Vienna. A five-year-old child of the parents is entirely normal. The birth of the patient was normal; she was nursed by the mother until the end of the second year. From birth lusty and lively; large, well developed; from the eighth month on the parents first remarked that the child did not take on more weight and since that time has remained at a standstill. The child has had an umbilical hernia since birth. It has never spoken.

Height, 62 cm.
Circumference of skull, 42 cm.
Breadth of shoulders, 45 cm.
Circumference of breast, 45 cm.
Pulse, 120.
Rectal temperature, 36°.

Panniculus adiposus soft, lax; myxedematous texture of the skin; walking and standing impossible. Forehead arched forward, root of the nose somewhat sunken in; no teeth as yet. Eyelids enormously swollen, tongue thick, abdomen markedly arched forward; umbilical hernia. Body weight 7.1 kg. From Dec. 2, 1909, on, thyroidin tablet every third day.

Nov. 10, 1910.—71 cm. long, weighs 9.1 kg. Treatment discontinued.

Entrance into the first medical clinic on Oct. 15. Can only stand when it holds fast on a support, cannot speak, is, however, otherwise lively and busies itself. All fontanelles closed.

Circumference of skull, 46 cm.
Circumference of breast, 50 cm.
Circumference of abdomen, 48 cm.
Anterior superior spine to internal malleolus, 30 cm.
Acromion to olecranon, 13 cm.
Olecranon to styloid process of radius, 12 cm.

Skin somewhat dry, no distinct myxedema. Root of nose sunken in only a little. Tongue always protrudes from the mouth; left anteriorly below, one tooth nucleus palpable, otherwise no teeth. Hearing apparently entirely normal. Thyroid gland not palpable; abdomen distended, liver is palpable, indication of umbilical hernia; the tickling reflexes of the external auditory meatus are present. Does not tell when she wishes to pass feces or urine. Nervous status, as far as elicited by tests, normal.

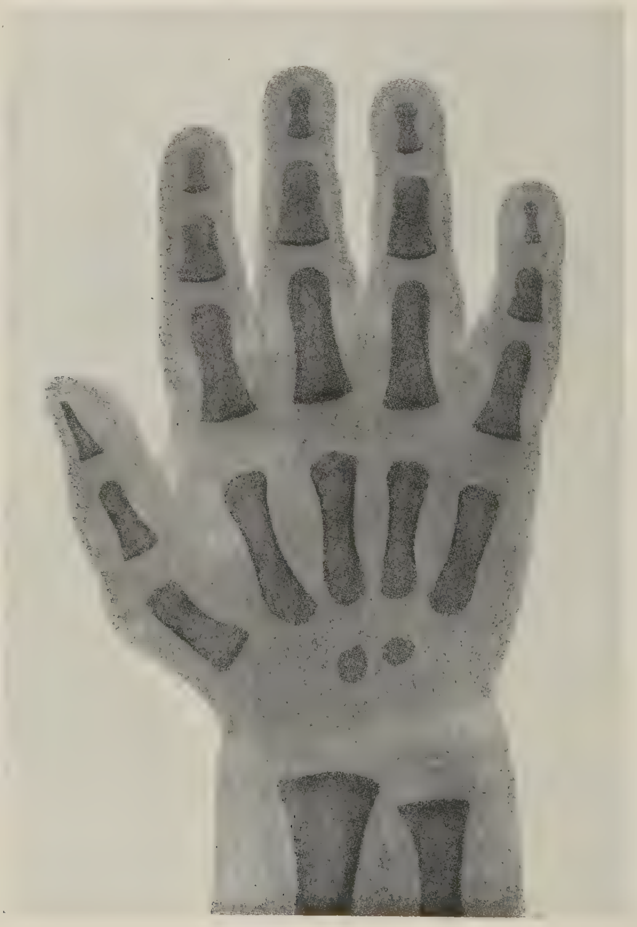

FIG. 12.—X-ray picture of a hand of a sporadic cretin (Observation XIV).

Patellar reflexes somewhat lively.

Oct. 15.—30 gm. dextrose, no sugar.

Nov. 11.—50 gm. dextrose, no sugar.

Oct. 24.—Erythrocytes, 4,560,000.

Leucocytes, 6800, of which:
Polymorphonuclear neutrophiles, 48.4 per cent.
Large mononuclears, 8.3 per cent.
Lymphocytes, 40 per cent.
Eosinophiles, 3.3 per cent.

Nov. 11.—Erythrocytes, 5,250,000.
Hb., 55 per cent.
Leucocytes, 8200, of which:
Polymorphonuclear neutrophiles, 38 per cent.
Large mononuclears, 37 per cent.
Lymphocytes, 54 per cent.
Eosinophiles, 4.3 per cent.

Nov. 26.—0.0005 gm. adrenalin subcutaneously and 50 gm. dextrose per os. After four hours 3.2 per cent. sugar.

Nov. 29.—One drop homatropine in eye; twenty-four hours later, still slight mydriasis.

Nov. 30.—Adrenalin, 0.0005 gm., no sugar.

Nov. 20.—0.005 gm. pilocarpine subcutaneously, weak sweat, no salivation.

From Dec. 2 on, two thyroidin tablets daily; from 6th on, three daily; from 8th on, five daily.

Dec. 14.—Pulse that was formerly 110, now 130; thyroidin medication now reduced to one tablet.

*Summary.*—We are dealing with a case of sporadic cretinism, probably depending on a congenital aplasia or hypoplasia of the thyroid.

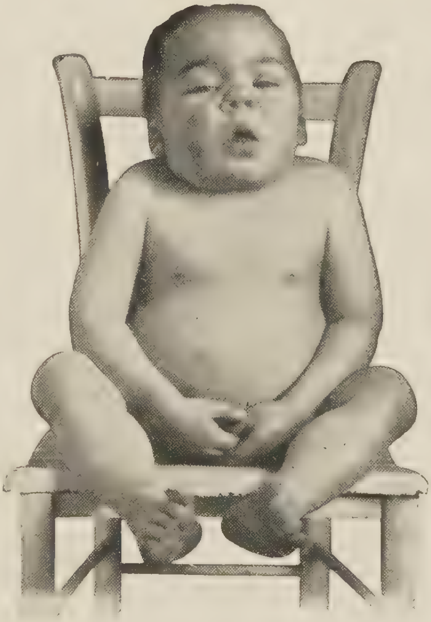

FIG. 13.—Sporadic cretinism.

Here are worthy of note the high assimilation boundary for sugar, the failure of adrenalin glycosuria, the strong action of atropine and the weak action of pilocarpine; there is, however, found an unusually high glycosuria on combination of dextrose and adrenalin. There occurs in this case a somewhat high tolerance for thyroidin.

Röntgen investigation of the skeleton of the hand, Nov., 1911: The bone-nuclei of the os magnum and the unciform bone are present. Those for the epiphysis of the radius and the basal epiphysis are still absent. The skeleton corresponds to that of a six- to eight-month-old child (Fig. 12).

Sella turcica corresponding to the size of the skull.

*Observation XV.*—Franz N. (see Fig. 13). Entered the psychiatric clinic of *Wagner* Oct. 6, 1909, four and one-half years old, from Rudoletz in Mähren.

The fourth child of healthy parents. Birth easy, at the right time. Head at birth already large. Speech up to the second year of life consisted of the simplest words only; words were such as tata, mamma, and since this time the child has not spoken much otherwise.

Parents and the entire family to the great-grandparents of the child have not suffered from goiter. Nowhere in the neighborhood does the father know of a similar case.

Length of body 85 cm., weight 19.2 kg. Head extremely large without, however, any hydrocephalic formation. Bones of the head of hard consistency. Strong development of the skeleton of the face. Very low forehead, eyes stand wide apart. Saddle-nose, epicanthus short, very broad cartilaginous nasal framework; cushiony lips; thick, broad tongue, that protrudes from the mouth. Cushiony ear lobes that lie close to the head. Cheeks very thick, throat thick and stubby. Thyroid not palpable. Thick lanugo hair on back. Skin of the body, especially in the supraclavicular grooves and on the backs of the hands and feet, springy, elastic; hands and fingers chubby. Abdomen much distended. Circumference 65½ cm. Reducible umbilical hernia. Reflexes as far as can be tested present. Noise tests were without any reaction.

From June 23 on was given one thyroidin tablet daily, until Oct. 24. Entrance into the first medical clinic. Now length of body 91.25 cm., weight 21 kg. Treatment is now discontinued.

Circumference of the head now 56 cm., circumference of the abdomen 65 cm., circumference of breast 49 cm.

Anterior superior spine to internal malleolus 44.5 cm.

Circumference of neck 36 cm.

Heart dullness somewhat broadened (also by X-ray, heart of characteristic spherical shape). Heart sounds pure.

Border of the liver palpable 10 cm. below the margin of the ribs in the mid-line, two fingers' breadth below in the right mammillary line.

Umbilical hernia about 3 cm. long, and its insertion 2.5 cm. in diameter. Penis very small, testicles have not descended. The child does not go to the toilet to void urine or feces. Slight heightening of the patellar reflexes, otherwise the reflexes normal. Nervous status, so far as can be tested, normal.

The child often stares into space for a long time, but at times is right lively and cries loudly. No trace of speech. Puts all objects into his mouth, even his own feces. Impressions of hearing entirely absent, no reaction of the eyelids to sounds.

Nov. 2.—50 gm. dextrose per os, no sugar. After several days 100 gm. dextrose of which he vomited a small amount, no sugar in the urine.

Nov. 9.—Erythrocytes, 5,480,000.
Hemoglobin, 70 per cent.
Leucocytes, 9000, of which:
Polymorphonuclear neutrophiles, 42.5 per cent.
Large mononuclears, 8 per cent.
Lymphocytes, 41 per cent.
Eosinophiles, 8.5 per cent.

A later count yielded:
Erythrocytes, 5,400,000.
Hemoglobin, 70 per cent.
Leucocytes, 11,000.
Eosinophiles, 12 per cent.

Nov. 21.—0.01 gm. pilocarpine. Sweat extremely slight, salivation negative.

Nov. 22.—Homatropine evinces weak mydriasis only, which however is positive after twenty-four hours.

Nov. 26.—0.001 gm. adrenalin subcutaneously and 50 gm. dextrose per os. After four hours 4.2 per cent. sugar.

Nov. 29.—Weak mydriasis forty-eight hours after installation of homatropine.

Nov. 30.—0.001 gm. adrenalin subcutaneously, no sugar. From Dec. 2 on, three thyroid tablets a day; from Dec. 5 on, five tablets daily; from Dec. 8 on, seven tablets daily.

Dec. 13.—Marked scaling of the skin, no trace of moisture, even of the palms.

Dec. 22.—Pulse irregular, only 72 to the count, although frequent abortive beats.

The dose was reduced to three tablets and after some days, when the pulse had become entirely regular again, five tablets were given continuously.

Jan. 8.—Leucocytes, 4800, of which:

Polymorphonuclear neutrophiles, 61.5 per cent.
Lymphocytes, 20.5 per cent.
Large mononuclears, 12.5 per cent.
Eosinophiles, 5.5 per cent.

Jan. 19.—The examination of the hearing now shows certainly that the patient reacts to loud noises. Distinct lid-reflexes.

March 29.—Thyroidin medication has now been continued in the large doses without producing manifestations of poisoning. The hearing is still better, the enlargement of the liver has essentially diminished in size; otherwise there is no change.

December 1910.—The nuclei of the os magnum and the unciform bone are alone visible in the carpus, while at this time the nuclei of the entire skeleton of the carpus should have been laid down. The epiphysis of the radius is present. The skeleton corresponds to that of a one and one-half to two-year child.

*Summary.*—The patient is from a goiter-free neighborhood. Also there exist no other grounds for the assumption of an endemic cretinism. We are indeed dealing with sporadic cretinism, probably dependent on aplasia or high-grade hypoplasia of the thyroid gland; and perhaps later there was added some other factor that we are not able to define that made the insufficiency still greater.

Thyroid medication here succeeded less than in the preceding case. It was also introduced much later. Apparently the thyroid insufficiency is here very much greater.

The investigation with adrenalin and pilocarpine several weeks after the discontinuation of thyroid gland therapy shows slight or negative action. The test as to alimentary glycosuria results negative. It is very interesting also that in this case adrenalin plus dextrose leads to an entirely usual degree of glycosuria.

Worthy of note in this case is the enormous tolerance for thyroidin and also the action of thyroidin on the disturbance of hearing and on the enlargement of the liver.

*Observation XVI.*—H. A., entrance into the psychiatric clinic (of *Wagner*) Jan. 21, 1909. Fifteen years old, female dwarf (95 cm.); face puffy, skin of the entire body myxedematous, dry and scaly. Supraclavicular fossæ filled with pad-like masses. Conjunctivitis eczematosa. Fundus normal. Circumference of skull 50½ cm. Root of nose sunken, tongue thick, also the lips, the teeth with transverse ridges, in great part carious, have remained very much behind in their development. Abdomen markedly distended, umbilical hernia.

Measurements.—Height, 95 cm.

Circumference of skull, 50½ cm.
Upper arm (acromion to olecranon), 19 cm.
Arm proper, 13 cm.
Lower extremity (spine [anterior superior] to heel), 46 cm.

Intelligence that of a four-year child. Can speak, can understand questions and statements addressed to her; can, however, not write nor read, and can say, of a prayer, only the words at the beginning. Weight 20 gm.

From April 27 on, 0.5 gm. sodium iodide, after which she became livelier; from June 8 on, one thyroid-gland tablet a day. Body weight at the beginning of July had gained 16.9 kg. The bowel movements, which formerly frequently occurred only every two or three days, have gradually become entirely normal. Rapid mental development. Is much more active, plays much, wants a looking glass, a net for her hair, begins to sing.

Jan. 18, 1910.—101 cm. Myxedematous texture of the skin much lessened, slight sweating of the palms of the hands. Dermographism.

Oct. 13, 1910.—The patient, sixteen and three-fourths years old, now enters the medical clinic. Length 110 cm., weight 23 kg. The thyroid-gland medication is now discontinued. Circumference of the skull 57½ cm.

Hair soft, skin somewhat dry, only the palms of the hands moist, tongue not enlarged, teeth much behind in their development. Circumference of abdomen 62 cm.; there still remain indications of an umbilical hernia. Liver palpable two fingers' breadth below the margin of the ribs. Pubis and axillæ entirely devoid of hair. External genitalia hypoplastic. Has never menstruated. The entire trachea is distinctly palpable, there is nothing to be felt of the thyroid. She gives correct information as to where she has been the last year. Cannot reckon, counting impossible.

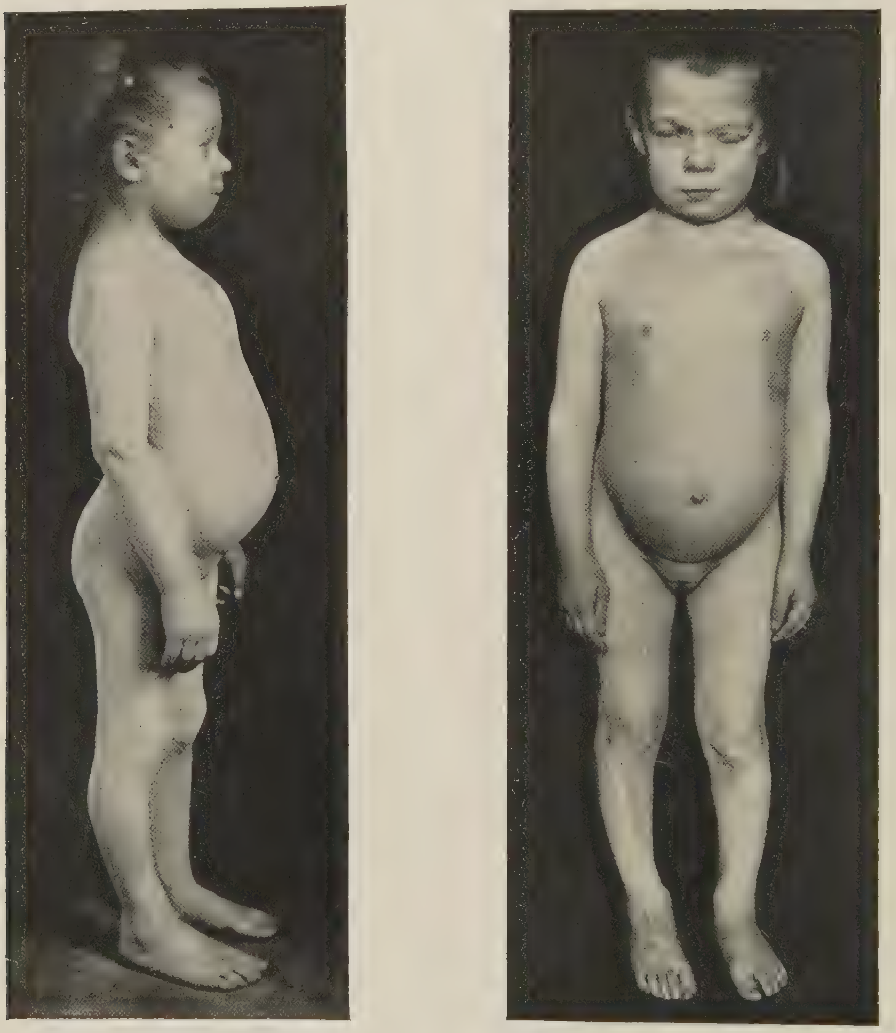

Fig. 14. Fig. 15.

Sporadic cretinism.

Oct. 15.—100 gm. dextrose, weakly positive.

Erythrocytes, 4,540,000.
Leucocytes, 11,200, of which:
Lymphocytes, 49 per cent.
Large mononuclears, 9.5 per cent.
Lymphocytes, 51.0 per cent.
Eosinophiles, 7 per cent.

Oct. 25.—100 gm. dextrose, no sugar.

Nov. 1.—Hands feel cool to the touch; patient has gained 1.7 kg. since her entrance.

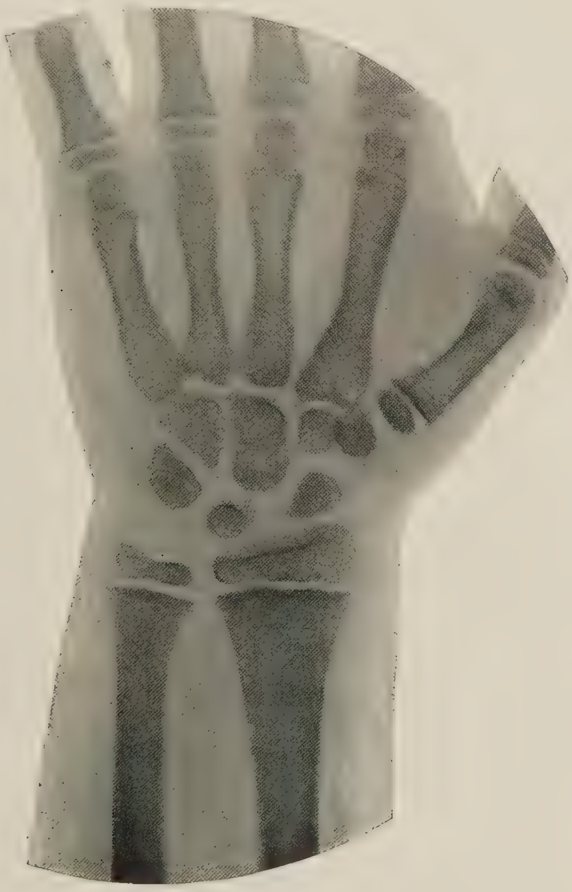

Fig. 16.—Sporadic cretinism, seventeen-year-old girl. In spite of a long-continued thyroid treatment the development of the skeleton of the hand belongs to that of a normal girl aged ten years (see Fig. 17).

Nov. 3.—Leucocytes, 12,100, of which:
Polymorphonuclear neutrophiles, 40.6 per cent.
Large mononuclears, 4.6 per cent.
Lymphocytes, 49 per cent.
Eosinophiles, 5.8 per cent.

Nov. 9.—Leucocytes, 11,500.
Hemoglobin, 65 per cent.

Nov. 10.—150 gm. dextrose, no sugar.

Nov. 16.—Skin entirely dry. 0.01 gm. pilocarpine; no salivation, only slight sweating.

Nov. 19.—Nervous status. Superficial abdominal reflexes increased and also plantar reflex lively; otherwise normal, as far as can be investigated.

Only very slight mydriasis after homatropine. On Nov. 22, 0.001 gm. adrenalin subcutaneously and 100 gm. grape-sugar by mouth. Minimal increase in blood-pressure, lasting only for a very short time. Pulse only 84 to 92. In the first two-hour period, no sugar; in the second, 4.25 per cent. in 15 cc. urine; in the next twelve-hour period, *Trommer* still strongly positive.

Nov. 26.—0.001 gm. adrenalin, no sugar.

Nov. 29.—Circumference of skull, 56½ cm., total height, 111 cm. Circumference of abdomen, 62 cm., circumference of breast (mammillæ), 64 cm., circumference of neck, 28 cm. Upper arm (acromion to olecranon), 21.5 cm., arm proper, 18.5 cm., lower extremity ([anterior superior] spine to heel), 52 cm.

Dec. 2.—Up to this time, pulse between 100 and 110. Bowel movements not entirely regular, in that one bowel movement is wanting every three to five days. From now on, five thyroidin tablets a day. From Dec. 6 on, seven tablets a day. Dec. 8, nine tablets a day.

During the next days the pulse rises up to 145 and sinks to its former count only on Dec. 22.

Leucocytes: 10,200, of which
Polymorphonuclear neutrophiles, 67.2 per cent.
Large mononuclears, 8.2 per cent.
Lymphocytes, 22.6 per cent.
Eosinophiles, 2 per cent.

X-ray examination of the hand skeleton. The epiphysial junctures of the fingers and metacarpal bones are still open. The skeleton of the carpus is as yet laid out in the form of round bone-nuclei. At this age the carpal bones should be fully developed, and the epiphysial junctures should be closing up (Fig. 16). Sella turcica corresponding to the size of the skull.

*Summary.*—Sporadic cretinism probably due to aplasia or high-grade hypoplasia of the thyroid gland. The thyroid-gland therapy instituted in the sixteenth year is able to affect the growth not inappreciably and to further intellectual development. That the marked inhibition of development that has existed for sixteen years cannot entirely be done away with is readily comprehensible.

The investigation of the carbohydrate metabolism showed that after the year-long administration of thyroidin the assimilation limits for grape-sugar lay abnormally low. It is very instructive that with the discontinuation of the thyroid medication the assimilation limits rose immediately, so that after several weeks as much as 150 gm. dextrose would be borne. Also adrenalin produces no glycosuria, while, on the contrary, adrenalin and grape-sugar produce abundant glycosuria.

An over-loading test with thyroidin showed that the tolerance in this case was at any rate rather high, as symptoms of poisoning first occurred only with large doses. Under the test with thyroidin, the number of neutrophiles rose considerably, and the assimilation limits for grape-sugar again sank rapidly.

In the *clinical picture* of sporadic cretinism the phenomenon most before the eyes is the *disturbance* in *growth*. Already *Buschan* collects from the literature thirty-four cases of sporadic cretinism that showed evident dwarfism. In the cases with high-grade disturbance of the function of the thyroid gland the length of the body was mostly below 1 meter. *Siegert* describes a two-and-a-half-year-old child of 50 cm. length; *v. Eiselsberg* a thirteen-year-old girl of 80 cm. length. In addition to the disturbance in the growth in height are found delay in the appearance of the bone-nuclei, and in the closures of the epiphyses (*Hertoghe, v. Wyss, Kassowitz, Diderle, Siegert,* and *others*). The original statement of *Virchow* that the calcification appears prematurely was later found to be incorrect; the case investigated by *Virchow* was one of chondrodystrophy (*Kaufmann*). This was further

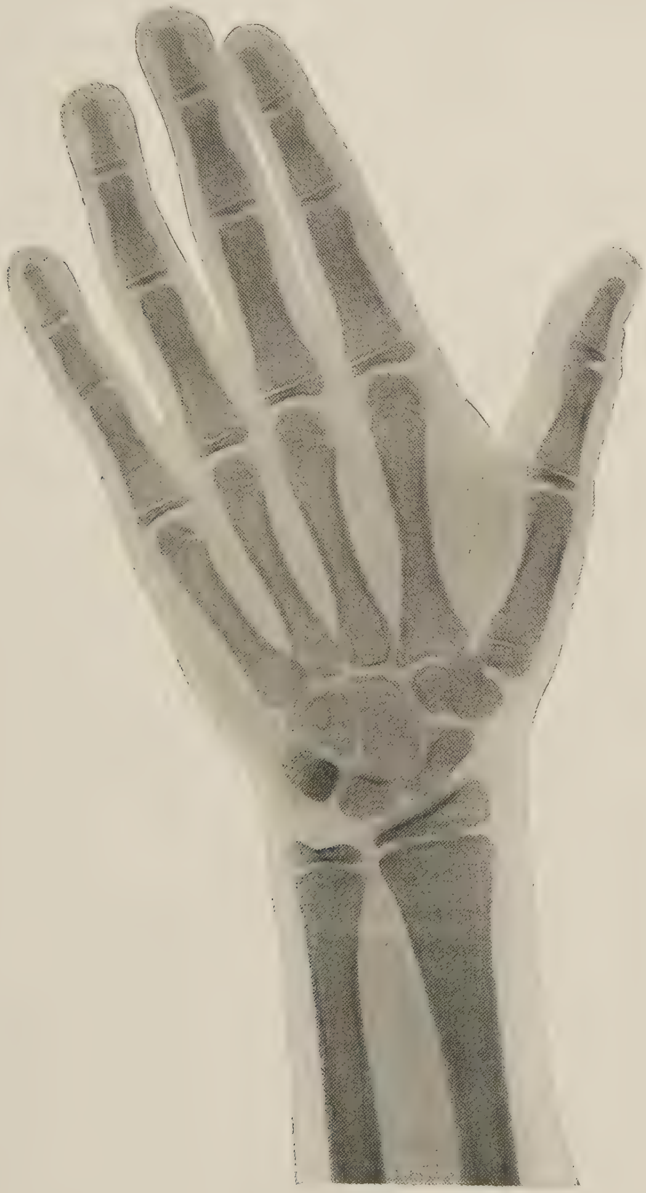

FIG. 17.—X-ray picture of the hand of a normal ten-year-old girl.

confirmed by *Weygandt* through the microscopical examination of *Virchow's* case.

Already *Argutinsky* had mentioned that the development of the bone-nuclei in sporadic cretinism is even more intensely delayed than is the growth in height. If, for example, the size of a twenty-year-old cretin corresponds to that of a six-year-old child, the retardation in the deposition of the nuclei lies even farther behind. In the pure cases with complete lack of thyroid gland the epiphysial joints do not succeed in closing. In the known case of *Bourneville*, autopsy, in the thirty-sixth year of age, showed epiphyses that were completely open. The closure of the fontanelles is markedly delayed. In the case mentioned the great fontanelle was still open in the twentieth year. At autopsy in the thirty-sixth year its place was filled by a translucent bony plate. Also *Kassowitz* mentions cases of infantile myxedema with markedly delayed closure of the fontanelles; thus in a thirteen-year-old individual he found the frontal fontanelles still distinctly open. The measurements of the bones, with regard to their thickness and length, correspond to the relations of childhood; this is then a *proportional dwarfism*, deviating from the normal proportions of childhood only in the development of the skull. The circumference of the skull does not indeed correspond to the age of the individual, but is distinctly larger than would be represented by the rest of the body structure. In addition there is a remaining behind in the growth of the vomer; this results in a *retraction of the root of the nose*, which lends to the face the characteristic cretinoid expression, which does not, however, reach the extreme grade as seen in chondrodystrophy. In the four-months-old case, with pure thyroaplasia, of *Diederle*, the measurements of the bones showed that they about corresponded to those of a new-born child. The disturbance in growth had therefore apparently first made its appearance after birth, and not already in fetal life. The *histological examination of the bones* in sporadic cretinism showed diminution in the size of the zone of cartilage proliferation, narrowing of the marrow cavity, abundant fat-contents of the marrow, and poverty of the marrow spaces in cells. Also according to *Diederle* there occurs a slowing of apposition and absorption in normal calcification. From this there results a certain degree of *sclerosis*. With this agrees the observation of *Kassowitz* and *Diederle* that the bones, when once formed, show an unusual hardness, in this respect differing from their condition in rachitis. The histological picture of the bones shows a certain senility; the disturbance depends on an equalized delay of the endochondral and periosteal ossification.

It is further characteristic for the disturbance in growth in sporadic cretinism that it reacts to thyroid therapy in a pronounced manner, even when the therapy is first begun after the twentieth year. We shall speak of this in the consideration of the therapy.

In the incomplete forms of sporadic cretinism the disturbances of growth are characterized by their slighter intensity. Here closure of the epiphysial junctures may occur, even in advanced years. I mention as example a case of *Magnus-Levy*, in which the treatment, instituted in the forty-fifth year—the patient was 132 cm. tall—failed to exercise any influence on growth, as the epiphysial junctures were already fully ossified.

*Disturbances in dentition* go hand-in-hand with those of growth of the bones. When the thyroid gland is entirely absent the children during the first year remain completely toothless. In the later years the milk-teeth develop very slowly and finally remain partially retained. (Often in addition to the retained milk-teeth are found the rudiments of the permanent teeth.) Here thyroid therapy, as we shall see later, may elicit excellent results.

*Umbilical hernia* is a constant finding in the higher grades of sporadic cretinism. *Kassowitz* observed it sixteen times in twenty-two cases of infantile myxedema. The eldest of these children was twelve years old. The hernia may attain the size of an apple. Therewith the abdomen is distended, the navel is markedly deep (*Argutnisky*), there is high-grade obstipation, which in the case of *Maresch* led to prolapse of the rectum. The *myxedematous* texture of the skin is for the most part distinctly evident; in the older cases, however, the skin is on the other hand *rather atrophic*, only the pad-like swellings of the supraclavicular grooves and the slight puffiness of the face, especially the eyelids, remain. For the most part the limit of the hair zone is far back on the forehead, to which are added protuberance of the malar bones, retractions of the root of the nose, cushiony lips, protrusion of enlarged tongue; all this lends the impression of something of an animal appearance to the face.

Inspection of the mouth shows that the palatine arches are for the most part high, deepened with furrows, the tonsils enlarged; and often in the pharyngeal space there are adenoids. The hypertrophic rhinitis which is present disturbs breathing; the children snuffle and snore; in most cases there is a discharge from the nose. In two of the above cases I found a distinct *enlargement of the liver*. Also in the case of *Argutinsky* there is the statement that the border of the liver was palpable two and one-half finger-breadths below the margin of the ribs.

It should also be mentioned that in the fully developed cases, the breathing is *extraordinarily slowed*. A twenty-eight-year-old case of *Magnus-Levy's*, who at the age of fourteen years had sustained a total strumectomy, breathed only six times in the minute.

The *sweat-inducing action of pilocarpine*, in the three cases cited, was very slight; salivation failed entirely; the mydriatic action of homatropine lasted very long.

The developmental *disturbances of the genitalia* are always very marked. In females the labia majora are stunted and do not cover the labia minora; uterus and ovaries are highly hypoplastic and the breasts fail to develop.

In males the penis is very small, the testicles do not descend at all or descend very late and in many cases are essentially smaller than in the normal individual. The pubic and axillary hair does not develop. With the failure of sexual maturity in boys, there occurs also the failure of the change of voice.

The *hematopoietic system* also suffers in development. The hemoglobin contents is for the most part much reduced, more than the number of erythrocytes. The behavior was very well illustrated in the three cases described although all three had been treated for a long time with thyroid tablets. For the most part the number of leucocytes is increased. The differential count of these shows an enormous reduction in the polymorphonuclear neutrophiles and a corresponding increase of the mononuclear cells, even when we consider that in children the number of neutrophile cells is smaller than in adults. The leucocytic picture shows the type of earlier stages of development (*Meunacher*). Among the mononuclear cells are found a great number of granular cells. Also *Türk's* irritation forms are observed (*Esser*).

The number of eosinophile cells is mostly very much increased. In my three cases the percentage was 12 to 33.

Thus the blood findings behave similarly to those of adult myxedemics, only the deviations from the normal are more strongly expressed. Also the pathologico-anatomical findings agree with this. While thyroidectomy in adult animals does not lead to a distinct alteration of the bone marrow, there has been observed by *Kraus* in young animals after thyroidectomy a lymphoid metamorphosis of the bone marrow; also *Aschoff* found in his case of thyroaplasia a lymphoid metaplasia of the marrow of the femur.

In sporadic cretinism, as in myxedema adultorum, there is found a paradoxical action of the thyroid substance on the leucocytic formula. While the administration of thyroid-gland substance in normal individuals increases the count of mononuclears at the cost of polymorphonuclear neutrophiles, we find in conditions of hypothyrosis under thyroid medication with the increase in hemoglobin and the number of red cells also an increase in neutrophile cells with a decrease in mononuclears. The abnormal forms vanish from the blood and the leucocytic formula approaches its normal constitution. In a case of juvenile myxedema (complicated with symptoms of deficiency on the part of the other ductless glands), I observed that the count of neutrophiles increased from 54 per cent. to 84 per cent. during a two-months' thyroid treatment.

*Esser* saw in a myxedemic child the count of neutrophiles increase under thyroid treatment from 19 per cent. to 41 per cent.; later, intoxication symptoms developed and with these the count of neutrophiles again sank to 19 per cent. I explained this case, that at first the thyroid medication exercised its usual favorable influence on the blood picture of hypothyrosis, but that later with the appearance of the intoxication symptom it assumed the character of hyperthyrosis.

In case N., Observation XV (sporadic cretinism), the neutrophilic count rose from 42.5 per cent. (Nov. 9) to 61.5 per cent. (Jan. 18); in case A., Observation XVI, from 32.5 per cent. (Oct. 15) to 67.2 per cent. (Dec. 22), under treatment with large doses of thyroidin.

Summarizing these observations, it may be said that on the absence or insufficient production of thyroid extract in the juvenile organism, the development of the hematopoietic system is severely inhibited. Agreeing with this is *Diederle's* observation that the disturbance in the growth of bone does not lie in the marrow of the epiphysial cartilage alone, but also in the bone marrow itself. Especially does the development of the neutrophilic cells suffer damage. There exists a slight grade of status lymphaticus that perhaps is in relationship with the faulty development of the chromaffin tissue.

The metabolism of sporadic cretinism has been carefully studied in the excellent investigation of *Magnus-Levy*. I reproduce from the table of this author the following figures:

| | Age, years | Length, cm. | Weight, kg. | Cc., $O_2$ | Cc., $CO_2$ | Cc., $O_2$ per kg. | Relation of the $O_2$ excretion to that of a healthy individual |
|---|---|---|---|---|---|---|---|
| Case I | 29 | 98.0 | 21.1 | 77.5 | 54.5 | 3.67 | 48 per cent. |
| Case II | 14 | 84.0 | 15.8 | 72.6 | 59.4 | 4.62 | 60 per cent. |
| Case III | 46 | 132.0 | 42.5 | 122.4 | 104.9 | 2.88 | 53 per cent. |
| Case V (light) | 14 | 131.5 | 29.5 | 154.1 | 137.0 | 5.22 | 96 per cent. |

In the fully developed form, the fundamental exchange is therefore much reduced.

With this agrees the experiment of *v. Bergmann*. He investigated the metabolism of a one-year-old child, employing the *Voit-Pettenkofer apparatus*. The child was put in equilibrium with a supply of calories that was far below that needed for a healthy child of like weight. Concerning the albuminous metabolism I shall refer to the chapter on myxedema adultorum. The salt metabolism in infantile myxedema is dealt with in investigations of *Haugardy* and *Langstein*. These authors found that in their case the assimilation of calcium amounted to about one-third of that of a normal child the same age. In this the intensity of the inhibition of bone growth finds expression in a pretty manner.

As concerns the carbohydrate metabolism, I might mention that in the three cases of sporadic cretinism that we investigated the assimilation limits for carbohydrates lay rather high several weeks after the withdrawal of thyroid medication. Also injection of adrenalin did not lend to glycosuria, while on the contrary injection of adrenalin with simultaneous administration of sugar always yielded strikingly high sugar percentages in the urine. Perhaps we may seek the cause of this in the fact that in sporadic cretinism also the development of the other ductless glands suffer damage on account of the disturbances appearing in early youth, so that the simultaneous overburdening of the alimentary and the nervous factors bring about an appreciable insufficiency.

The reduction of the metabolic processes expresses itself, also here as in myxedema adultorum, in a *hypothermia*. For the most part the temperatures lie near 36°; also in my cases, was the level of temperature low.

In his case *Diederle* found during the last week of the life of the patient 33.4°. Also an increase of temperature may remain absent when infectious processes occur. However, this is not usually the case. In the case of *Bourneville*, already mentioned many times, the temperature during a case of erysipelas rose to 40° Celsius.

The statements as to the behavior of the hypophysis in sporadic cretinism do not agree. Extirpation of the thyroid gland in young rabbits leads to enlargement of the hypophysis (*Rogowitsch*, *Gley*, and *others*). Microscopical alterations of an apparently degenerative nature have been many times described. Also in many cases of sporadic cretinism the hypophysis or the sella turcica is enlarged. In my case, however, the X-ray examination of the skull showed no enlargement of the sella. *Schilder* likewise found in his three cases of thyroaplasia no enlargement of the sella; but on microscopical examination he found peculiar cells that approached near to the so-called "pregnancy cells" of the hypophysis.

In sporadic cretinism the thymus gland often seems hypoplastic; *Pineles* found thyroaplasia and thymus aplasia combined. *Bernheim-Karrer* and *Rucacz-Gruchet* found only slight rests of the thymus. Other observers found the thymus normally developed.

The marked inhibition in the development of the osseous and the blood systems and the ductless glandular system would lead us to expect that there would also be something wanting in the development of the *central nervous system*. This in the high-grade cases expresses itself not only in the absence or remaining backward of the mental and psychical development, but even in the inability to carry out the movements that subserve finer coordination. As *Kassowitz* observes, the children learn late to balance their head, to sit, and to walk.

Such cases, as for instance the case of N. described (Observation XV), have almost nothing human left about them. They give utterance to only some inarticulate sounds and almost every sign of mentality is absent. They do not go to the toilet to void urine or feces. N. always devoured his feces whenever he could get access to it. In lighter cases the disturbance of mental development is somewhat shorter. Usually the sense of smell is well developed.

The statements as to *disturbances of hearing* in sporadic cretinism are very diverse. The assumptions as to the cause of these diverge greatly. It is certain that the absence or insufficiency to the function of the thyroid may lead to disturbances of hearing. I refer to the results of thyroid medication that are often attained in a striking manner in these cases. It is just as certain, however. that with complete failure of the thyroid gland the organ of hearing may be completely developed from birth on. *Siebermann* examined the organ of hearing in *Diederle's* cases of congenital thyroaplasia and found entirely normal relationships in an anatomical sense. Even in a functional sense, disturbances do not necessarily have to be present—for *Maresch's* case of thyroaplasia showed no deafness. Hence what is under dispute is only how to explain the disturbances that occur in many cases. *v. Wagner* was the first to express the opinion that myxedematous swelling of the mucous membrane of the tympanum, the Eustachian tube, etc., could furnish the cause of the hardness of hearing. On the contrary, *Denker* states that thyroidectomized animals after operation are completely deaf, show on histological examination no myxedematous alterations of the mucous membrane and the organ of hearing, nor any degenerative alterations in the nervous organ of hearing or in the bulbar centers. The hypothesis of a dysthyric hardness of hearing (*Bloch*) is therefore denied. It is feasible to think, as many otologists assume, that central perception of the stimulus of sound suffers. There is then concerned a form of cortical deafness, or that form of deafness which *Heller* describes as psychical deafness, in which the perception of words does not come to consciousness, or as *Gutzmann* suggests, serious defects of attention or a high-grade weakness of memory for speech make their perception of words entirely impossible. Not entirely easy is differential diagnosis from sensory aphasia. The distinction is made possible only by the characteristic signs of feeble-mindedness. One of my cases (case N.) seemed to be deaf-and-dumb. This was striking as otherwise complete hearing mutism [Hörstummheit] does not seem to occur in sporadic cretinism. The ear tickling reflex was present. From the side of the specialists, hearing mutism [Hörstummheit] has been assumed (*Dr. Fröschels*). The conception of hearing mutism is not, however, uniform among otologists. *Gutzmann*, *Nadoleczny*, *H. Stern* and *others* speak of hearing mutism only when it concerns individuals (mostly children from third to seventh year) who are mute in spite of intact intelligence and intact hearing. These cases of pure hearing mutism are not common. In the case of N. there indeed occurred, after several months' treatment with large doses of thyroidin (to seven tablets a day), a slight, but distinct, degree of ability to hear (lid reflex). Unclear however remains the circumstance that also in complete absence of thyroid gland from birth, deafness does not always develop; as has already been mentioned, there occur cases of thyroaplasia *that heard*. Also I should not neglect to mention that in the numerous dogs on which I myself performed thyroidectomy, and on which later exact investigation disproved any existence of accessory thyroids, there were never to be observed perceptible mutism even after a period of observation lasting up to two years. The question still needs careful study.

In cases in which the power of hearing is markedly affected or is absent, the development of speech is of course also slight; in the case mentioned, case N., it was limited to a few inarticulate sounds.

We know nothing as to the etiology of thyroaplasia and thyrohypoplasia. *Pineles* states that there are sometimes malformations, tuberculosis, or alcoholism in the ancestry, but this statement does not explain much. For infantile myxedema, all those damaging influences come into consideration that were set forth for myxedema adultorum. Worthy of note is the statement of *Spolverini*, that sucklings who were nursed by women with goiter developed myxedema. All of *Spolverini's* observations, however, do not seem to me to be free from objection. It seems well in this case for us to assume an expectant attitude, until more observations have been made. The thyroid secretion does not seem to go over in the milk, as according to many observations (*Lange* and *others*) it was found that sucklings who were nursed by healthy women, might yet develop myxedema.

**Differential Diagnosis.**—In the diagnosis of infantile myxedema all those points are to be considered that were mentioned in the diagnosis of myxedema adultorum. To these are added in infantile myxedema the ear marks of the remaining behind in the physical and the mental development. Among these the inhibition of ossification is especially important. *Siegert* is justified in emphasizing this. One should not forget, however, that in many vegetative disturbances, that have nothing to do with the thyroid gland, a delay in ossification may exist. As far as it affects only the closure of the epiphyses, as for instance in the case in eunuchoidism, it offers no difficulty from the standpoint of differential diagnosis, as in infantile myxedema the delay in growth and that in the occurrence of the bone nuclei is very evident On the contrary, there occurs in true infantilism and in hypophysial dwarfism an entirely similar, although in most cases not so severe, a delay in ossification as in infantile myxedema. It is true that growth in infantilism may sometimes be hastened through thyroid medication, but not in such a manner as in sporadic cretinism. Hypophysic dwarfism tends to behave similarly (see Chap. VI). In both conditions, moreover, the assimilation boundaries for thyroidin lie essentially lower than in sporadic cretinism.

The distinguishing of the etiologically different forms of cretinism in vivo is often difficult, and in many cases quite impossible. Light cases, or those in which the delay in development sets in at a later stage are to be counted with those of infantile myxedema. In the severe cases that occur quite early the assumption of a thyroaplasia is better warranted, but is not to be relied on in vivo, as the negative finding on palpation is valueless.

We shall consider in the third chapter the delimitation from endemic cretinism.

## Treatment of Athyrosis and Hypothyrosis

Light grades of thyroid insufficiency may heal spontaneously or under the use of thyroid gland tablets (probably through the stimulating action of the iodine they contain on the thyroid and through the raising of all metabolic processes). In the severe cases and especially those with complete absence of the thyroid, an ideal therapy would be the *implantation of a new thyroid gland.*

Already *A. Schiff* tried to remedy the deficiency, in animals in whom the thyroid gland had been extirpated, by the implantation of a new thyroid. *H. Bircher* was the first, in 1889, to succeed in the implantation of a thyroid in a case of very severe cachexia strumipriva.[1] He implanted with good results a human thyroid into the abdominal cavity; there soon, however, occurred a relapse. A new implantation brought about considerable improvement, indeed even there was a return of the menses, which had ceased for a year; but this result too was not permanent. Later *Collins* and *Macpherson* reported results lasting from one and one-half to two years in myxedema. In these cases there were many renewed transplantations. Even more favorable results are reported by *Gibson* and *others* in sporadic cretinism. *Horsley* proposed that thyroids of monkeys or sheep be transplanted under the skin of the breast, *Rehn* under the skin of the throat. New hopes were aroused by the attempt of *Payr* to transplant thyroid tissue into the spleen, at first in animals, later in a four-year-old case of sporadic cretinism. In the case last mentioned the thyroid tissue came from the mothers. There occurred an essential improvement which affected, in addition to the myxedematous symptoms referable to the skin, also the intelligence and the growth of bone (12 cm. in five months). But also in this case the result was not permanent. *Kocher* suggested transplanting thyroid gland into the bone marrow. *Moszkowicz* implanted thyroid gland tissue into the tibia of a six-year-old myxedematous child. Here too the result was good, but only transitory. (Personal communication.) Also the results attained by *Benmann* seem to have been only transitory.

New hopes have been awakened through the important investigations of *Carrel* on the suture of vessels. *Stich* and *Makkas* succeeded in doing autoplasty on dogs; heteroplasty did not however succeed. Also *Enderlen* and *Borst* come, on the ground of their interesting experiments, to the conclusion that autotransplantation, that is, the transplantation of the thyroid gland from one part of the body to another of the same individual represents permanent results. Already homiotransplantation, that is the transplantation of the thyroid gland of an individual to another of the same species, for instance, from dog to dog, or from goat to goat, remained without results even when the animals were from the same parents. The vessel suture indeed healed, the vessels remained patulous, the glands however became absorbed. Experiments on cretins likewise led to negative results. The thyroid artery and vein from the upper pole of the thyroids obtained from struma operations on man were united to the axillary vessels of the cretins; but here also there came about a gradual absorption of the glands. *Enderlen* and *Borst* come to the conclusion that already the slight biochemical differences that exist between the tissues of different individuals of the same species are sufficient to prevent a permanent functionating of the engrafted organ.

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[1] The experiments of *v. Eiselsberg* are of extraordinary interest for tetany and will be considered under that caption.

Therefore the *sovereign method of treatment to-day is still the administration of thyroid-gland substance.*

*Murray* first proposed the treatment of myxedema with carbolated glycerin extracts from the thyroids of animals and practised this with good results. Also *Kocher*, *Leichtenstern*, *Ewald*, and *others* saw good results. Since that time, however, *Fox*, *Mackenzie*, and *others* found that they could succeed in inducing the action of the active principle also by administering it by mouth; this method superseded all others and to-day is alone practised. At the beginning one saw individual cases of severe acute intoxication. In many of these death occurred with profuse diarrhea after the ingestion of a very slight amount of thyroid-gland substance. Here the effect must have been due to putrefied preparations, as the symptoms deviated from those of thyroidin and the latter appeared only after the ingestion of much larger doses.

Of the numerous thyroid-gland preparations that are found on the market to-day the tablets of *Burroughs, Wellcome & Co.* (England) and those of *Parke, Davis & Co.* (America) are characterized by the intensity and uniformity of their action. They consist of dried sheep thyroid and come on the market in doses of 0.1–0.3 gm.

Of other preparations I mention the thyreoidinum siccatum (*Merck*), thyraden (*Kocher*), in pills or tablets representing 0.0007 gm. iodine, and iodothyrin or thyroiodin (*Bayer*). 1 gm. contains 3 mg. active substance or 0.3 mg. iodine, representing the iodine content of 1 mg. fresh lamb's thyroid.

According to the investigations of *Fonio*, the action of thyroid preparations on the metabolic processes (albumin decomposition, diuresis, body weight, etc.) parallels their iodine content. This does not hold good for all actions of the thyroid-gland substance. For instance there occurred in my own experiments with iodothyrin in every dose (to 7 gm. daily) action on the metabolism much greater than that on the cardiovascular apparatus. We also really need much larger doses of iodothyrin than of tabloids to induce symptoms of hyperthyroidism. In his substitution experiments *Magnus-Levy* ascribes to iodothyrin the same activity as that of thyroidin. It is quite undoubted that iodothyrin exerted a powerful influence on the fundamental exchange of *Magnus-Levy's* patients—yet we cannot make out from *Magnus-Levy's* protocols whether on long-continued administration also the influence on bone growth was the same. According to this it is not at all likely that, as *Pick* and *Pineles* state, in young thyroprivic dogs the symptoms of deficiency are not fully combatted by iodothyrin but that they are combatted by the English tablets.

Thyroantitoxin, potassium iodide, and hypophysis substance are, as shown by the experiments of *Magnus-Levy*, entirely actionless.

As far as the dose is concerned, it is well in every case to begin with small doses and gradually to increase. In adults we give one to two English tablets daily and can gradually increase to from three to five. If we have attained a favorable result, we may again decrease the dose to two or one tablet. Children are usually first given one-half tablet, which may be increased to from two to three tablets. In my cases of sporadic cretinism I went transitorially as high as seven tablets, in one case indeed to nine. *Kassowitz* recommends thyreoid elixir (*Allen Hanbury*, London) of which one coffee-spoonful represents about one-sixth of a sheep's thyroid gland. Children under a half year should be given one-half coffee-spoonful daily, later increased to one coffee-spoonful. Only in children over twelve years of age did *Kassowitz* order up to two coffee-spoonfuls per day.

The result of thyroid-gland medication in *myxedema adultorum* is in the most cases an immediate one. The myxedematous swellings may undergo an appreciable reduction even in a few days. Together with this there goes for the most part, a loss of the body albumin, that for the most part depends on the rapid melting down of the myxedematous tissue. In the cases in which very marked swellings have occurred, the skin is lax and wrinkled. Very rapidly also does it act on the secretion of sweat, in that the previously dry skin becomes moist; then too, the marked scaling ceases. The action on the trophic disturbances naturally takes a long time, but are no less striking. The bald spots on the head cover again with new hair; the hair on the axillæ and on the genitalia become thicker, the hairs again feel soft and pliable. The pulse becomes more rapid, the albumin exchange and the fundamental exchange rise to normal, the appetite increases, the beginning loss of weight supersedes the gradual increase in weight. The diuresis becomes more abundant, the lowered temperature rises at first somewhat above the normal, and then shows a normal level. The action on the blood is usually slower; it usually requires a medication of several weeks' or several months' duration before the red cells and the amount of hemoglobin come back to normal and before the differential counts of the white cells show normal values. The mental condition improves much more rapidly. The apathy may appreciably improve after only a few days, the patients become more active, they take a more active interest in their environment, and the memory improves. Also the mental disturbances accompanying the myxedematous condition show a pronounced improvement and under the thyroid medication may even become entirely normal. In the case of *Pilcz* already mentioned the illusive ideas disappeared entirely; with the withdrawal of the medication the myxedema and also the mental disturbance recurred. A renewal of the therapy again brought about cure, that remained definite in spite of discontinuation of the treatment. This patient had a goiter. *Pilcz* supposes that in this case the thyroid gland regained its activities through the stimulating influence of thyroid medication. Also the hardness-of-hearing sometimes accompanying myxedema often shows a decided improvement. Already the English Myxedema Commission found that among one hundred and nine cases of myxedema, nearly the half showed disturbances of hearing, that disappeared under thyroid treatment. Also speech becomes livelier indeed at the beginning of treatment, as *Magnus-Levy* states. In many of the cases stuttering appears at the beginning of the medication. *Gutzmann* explains this in the fact that the desire for speaking becomes rapidly increased, while there is a certain awkwardness of speech due to inhibition of the peripheral speech mechanism (swelling of the mucous membrane of the mouth, the nose, the throat, and slight mobility of the velum palati). Also the disturbances in the sexual sphere improve often astonishingly. The dysmenorrhea disappears, the long-absent menstruation may recur, in men potency may again return. Existing albuminurias tend to disappear under thyroid medication.

The results of thyroid medication in typical cases is to be regarded as almost certain. Already *Heinzheimer* has collected one hundred and fifty cases from the literature in which a complete favorable result was brought about by the treatment. Cure can occur even when myxedema has existed for a long time. In a case of *Dunlop* the myxedema had existed for twelve years.

In the cases of formes frustes of myxedema the results are just as satisfactory. Especially in the cases of thyrogenic obesity, thyroid medication, as already mentioned, brings about, with diet freely chosen and with improvement of the general conditions, a rapid reduction in weight, while marked reduction of the caloric supply only produces conditions of weakness.

Sometimes, indeed, the results of thyroid medication in myxedema are not so revolutionary. In the first place it may happen that on account of the long duration of the disease more deeply seated disturbances have developed, for example, high-grade anemia, which then furnishes a slight resistance to the administration of thyroid gland. In other cases symptoms of thyroidism rapidly appear, that call for the limitation or eventually the discontinuation of the agent. In such cases it may happen that the symptoms of myxedema are only a little influenced while tachycardia, insomnia, excitation, etc., make their appearance rapidly. Such a case was first described by *Béclère*. Here the myxedema gradually disappeared. There occurred, however, rapid loss of weight, tachycardia, insomnia, excitations, polyuria, albuminuria, partial paraplegia, sensation of heat, sweats, tachypnea, transitory tremor, and a slight grade of exophthalmus.

*Mabille* believes that the simultaneous administration of small doses of arsenic prevents the occurrence of symptoms of hyperthyroidism. *Ewald* agrees with him. *Magnus-Levy* missed this action of arsenic. *Hertoghe* warns against the administration of alcohol or morphine during the thyroid medication. He recommends administration of sodium bicarbonate, or, when diarrhea occurs, of bismuth.

In general we may well assume that typical cases of myxedema show a high tolerance for thyroidin. When manifestations of thyroidism occur, the cause of these may lie in a simultaneous degeneration of the heart muscle, that reacts more quickly to thyroid medication, or we are probably not dealing with typical myxedema, but with a combination of myxedema symptoms with symptoms of deficiency on the part of the other ductless glands (see multiple sclerosis of the ductless glands).

The action of thyroid medication in *sporadic cretinism* deviates in many points from that just described. On the one hand, there here occurs a number of other disturbances which relate to the existing disturbances in development (growth in size, dentition, sexual sphere, etc.); on the other hand, it is intelligible that with the long existence of the inhibition of development degenerative conditions have become established that are no longer reparable. Very significant results are hence to be expected only in light forms or when the treatment has been started early. Very significant seems to be the *influence on growth.* Already in 1896, *Buschan* collected from the literature thirty-two cases which showed rapid growth under thyroid medication. Latterly, statements as to this subject have considerably increased.

X-ray examination shows that with the increased growth in height there occurs rapid appearance and growth of the bone nuclei, or rapid ossification of the epiphysial junctures.

*Hertoghe* states that in myxedematous children under certain circumstances, administration of thyroid may lead to such a rapidly increased growth in height that scoliosis or kyphoscoliosis develop. In the fully developed form of sporadic cretinism in which the epiphysial junctures are often fully open in the third and fourth decade, there may still occur under thyroid medication, appreciable growth in height and finally closure of the epiphysial junctures and the fontanelles.

As is the case with ossification, the previously retarded dentition also shows a sudden acceleration. I cite from the reports of *Kassowitz* the following example: A twenty-two-month-old child had not a single tooth; after a six months' treatment sixteen teeth had erupted. A similar accelerating influence is exercised on the formation of the permanent teeth. A ten-year-old girl had only remnants of the milk-teeth; after one year's treatment she possessed six, after two years' treatment eighteen permanent teeth. Very pretty examples of the stimulation of growth through thyroid medication are found also in *Oppenheim's* text-book of neurology and in *Siegert.*

Under the influence of the medication there disappear, not rarely in a few weeks, sometimes after a month, the umbilical hernias. These are almost constant in infantile myxedema, and often appreciably large in size.

Just as significant is finally the influence on the genitalia and the secondary sexual characters. *Magnus-Levy* reports the case of a forty-five-year-old cretin, in whom at the beginning of medication the pubic hair began to develop and the genital member began to increase in size. In a case of cachexia strumipriva, in whom the struma had been totally extirpated at the age of fourteen, thyroid medication was begun in the twenty-eighth year. Already after two years there was noticed a certain sexual development, after seven years all sexual characters were present and sexual maturity was attained. In the fully developed form of sporadic cretinism it is not, of course, to be expected that a late-introduced treatment is able to bring about procreative capacity.

Also the mental development takes part in this general impetus.

In the severe cases of infantile myxedema permanent administration of thyroid substance is necessary; when the therapy is discontinued relapses occur, even when the administration of the larger doses have transitorially brought about symptoms of hyperthyroidism (*Knöpfelmacher*). In slight cases the result is mostly a permanent one; in such cases we assume that under the stimulating influence of the therapy the thyroid gland has held fast to its development, or the less altered parts have recovered.

*Thyroid therapy has been tried in a great number of disease conditions that have nothing directly to do with myxedema and is often very much valued.* As to its value in obesity I shall come to speak in the consideration of the various forms of obesity at the end of this book. Also as to its influence in diseases of the hypophysis, the sexual glands, infantilism, and multiple sclerosis of the ductless glands, I shall refer to in the appropriate chapters. Very much under discussion is the use of thyroidin in the treatment of **scleroderma.** Since *Singer* first reported as to the favorable results a series of good results have been published. In other cases there were soon manifested symptoms of thyroidism with only slight improvement of the sclerodermic symptoms, in other cases, finally, the treatment failed entirely. The literature as to this subject is found in detail in *Cassirer's* communication. *v. Notthaft* is of the opinion that favorable results, where they have been obtained, depend only on the stimulation of the general metabolism (consult also the statements as to the ductless gland theory of scleroderma in the first chapter). As to therapeutic results in endemic cretinism see the next chapter.

## Addendum

With regard to inflammations of the thyroid, cases of acute idiopathic thyroiditis have been reported by *Dutrow* and *others*. In *Dutrow's* case, which was accompanied with a leucocytosis of 12,000, prompt relief was obtained on incision. In the majority of cases, such energetic treatment will not be necessary. The application of cold to the neck in this case is a means of physical treatment that must not be forgotten or dispensed with.

The question of dysfunction in the cases of Basedow's disease has by no means been disposed of, and in America has attracted no less an authority than *Halsted*, who has been much impressed with recent experiments of, among others, *Klose*, *Lampe*, and *Leisegang*. *Lampe* has been active in applying to the sera of Basedow's patients the Abderhalden reaction, with various organs as the objects to be acted on, with the result that he finds present in the sera ferments against ovaries, thyroid, thymus and no other organs. *Deutsch* has also experimented along these lines and has found that thymus gland tissue is split up also by normal serum. The significance of these experiments would seem to point to some defect of thyroid secretions; whether or not the positive results of the experiments mentioned above would tend to rule out simply a mere excess of thyroid secretion is not known to the translator.

The fact that the sera act on ovaries in the Abderhalden test would point to some defect in ovarian action. It is well known that Basedow's disease is often associated with, in addition to the menstrual disturbances that seem to be a part of the disease itself, pelvic disturbances, and that the disease is often considerably ameliorated, if not cured, with the remedying of these pelvic conditions. This fact has been repeatedly pointed out, and is mentioned among others by *Porter*. According to *Lampe*, dysfunction of the branchiogenic organs leads to dysfunction of the sexual glands. In some women, there is no doubt that the pelvic or the sexual trouble has led to marital unhappiness, this even when there is no gross gynecological lesion. According to *Thomas*, who in speaking of the subjects of exophthalmic goiter states that "nearly every married woman with whom I have discussed the matter has admitted some sort of incompatibility with her husband, and since it almost always appears during the active sexual life, I strongly suspect a distinct relationship."

The transition into the sexual sphere leads us once more into the confines of the Freudian hypothesis. Scarcely any of the most ardent of the advocates of *Freud* would venture the assertion that Basedow's disease is the result of a suppressed sexual experience of childhood, yet such a Freudian disciple might find evidence for it in a case of Basedow's in a child fifteen years old, that I saw at the St. Agnes Hospital, Philadelphia. This child had been the victim of an attempt at rape, immediately after which it developed the classical symptoms of Basedow's disease (I am not certain as to the presence of an enlarged thyroid) and almost utter inability to speak, which symptoms had persisted for some months. I am not certain as to the ultimate fate of the child, as she had been referred to the hospital from a country district, and paid only one visit to the hospital.

It is evident that in the above case the sexual element if present at all was subordinate to that of the factor of fright, which was present in the present case, seen by me at the St. Agnes Hospital. It was that of a highly religious, intelligent married woman, M. H., aged twenty-nine years, who during the strain of nursing a sick father, who subsequently died, sustained a fright, during which she found that a burglar had entered her store. A few weeks later her father died. Since the time of his death she suffers from obsessions of a religious and "immoral" nature, in the course of which she dares God to do his worst by her, and wishes harm to people. Sometimes the obsessions are of a sexual nature, and objects in her environment suggest to her thoughts that she is ashamed of. The patient dreams very much, but none of the dreams have a sexual content, at least so far as she states. Since the onset of the dream her mental and physical conditions have improved somewhat, in consequence of a stay at a sanitarium. She has been happily married for five years, shows a moderate amount of libido (it increased very little during the earlier stages of her illness), but has had no children, not because she uses means to prevent conception, but because according to a doctor her "womb is turned." There is in a case some evidence of hyperthyrosis, fine tremor, pulse 112, rather large thyroid, suggestion of exophthalmos, leucopenia of 2000 and various accessory signs (tendency to looseness of bowels rather than constipation, hair has become finer and more luxuriant).

The factor of fright in the etiology of Basedow's disease has been emphasized by *Crile*, whose name is important in the ductless glandular diseases in general, not only because of the fact that he has developed an ingenious theory for the explanation of certain of these diseases (especially Basedow's disease) but also because of his theory and practice of treatment in operating on Basedow's disease and in general (principle of anoci-association). *Crile* agrees with the author that Basedow's disease is conditioned by a state affecting the central nervous system, in the course of which the nerve cells of the cerebral cortex become chromatolytic, at the same time that the cells of the liver and the suprarenals become less granular. These organs together with the thyroid gland, and the muscular elements constitute the kinetic system, the purpose of which in the organism is the conversion of potential energy into kinetic energy. The above changes, if I understand *Crile* rightly, are more or less theoretical for Basedow's disease, but have been obtained by him in a number of conditions such as the various forms of traumatic, emotional, and toxic, foreign proteid, and anaphylactic shock, as well as in various forms of drug poisoning and anemia. As has been stated, *Crile* has formulated on the basis of theory his principle of anoci-association upon which is founded a method of operating in which the deleterious effects of shock are minimized by a combination of local and general anesthesia. The method has been applied especially to operations on the thyroid gland. Whether or not the good results attest to the truth of the theory, or whether the combination of the two forms of anesthesia summate in some other way is of theoretical importance; practically, the good results speak for themselves, and are attested to by *Frazier* and *Müller*. The method is attended with a number of refinements of technique for the consideration of which the reader is referred to *Crile's* work. One of the important factors is a sort of psychic treatment, consisting in the fact that the patient is gradually habituated on successive days to the method of general anesthesia, while under the impression that he is receiving treatments. As has already been stated at another place *Crile's* theory is based on observations on 40,000 nerve cells, and forms an interesting explanation for the rôle of the central nervous system in the etiology of Basedow's disease.

The effect of thyroid secretion on the central nervous system, the close connection of the central nervous system with the thyroid is instanced in the association of epilepsy with thyroid disease, especially exophthalmic goiter. This association which is acknowledged cursorily by *Kocher* and *Cushing* was pointed out by the translator some time ago. It is interesting that a short time after the translator presented his cases *Potts* allowed him to present the history of an adult female who developed epileptiform convulsion for the first time after the use of double the prescribed doses of thyroid extract. It is probable that in this case and in some of the cases previously reported by the translator, the thyroid-gland substance acted as a toxic agent on a central nervous system already predisposed to the occurrence of epilepsy. It is interesting, however, that the thyroid extract is one of the metabolic products that acts in this way.

With regard to the laboratory symptomatology of Basedow's disease, *Kocher* has corroborated his conclusions as to the blood picture in Basedow's disease by over 670 cases that have been operated on. He regards the blood examination as of the greatest diagnostic importance in light and obscure cases of Basedow's and myxedema. In 155 cases of myxedema there were only twenty-six that did not show a leucopenia. The degree of absolute leucopenia is more considerable than in Basedow's disease, lying between 3000 and 6000. Lymphocytosis lies between 30–40 per cent. less than in Basedow's disease. The mast-cells are 0.2–0.4 per cent. In myxedema the coagulation time is decreased, to as low as six minutes. This hastening of coagulation time is very constant. The blood picture approaches the normal with favorable therapeutic procedures.

Cases of diffuse colloid goiter approach the type of blood picture of myxedema. Nodular goiters show, as a rule, a normal blood picture, or, occasionally that of hyperthyrosis.

This blood picture has been much discussed, and is worthy of even more close study than it has received, especially in view of the more recent studies of the pathology of the thyroid gland in goiter by *Wilson* and by *Plummer*, stated below.

*Fonio's* experiments have shown that when thyroid or colloid goiter or Basedow's struma preparations are administered to myxedemics there occurred an increased elimination of nitrogen, increased diuresis, and decrease of the body weight, and that the nitrogen elimination varied directly as the iodine content of the preparation administered. In the two cases he worked on, he was unable to substantiate a hyperleucocytosis or an eosinophilia.

In passing, the translator would state that in America the condition myxedema seems to be relatively rare.

So far as the pathology of the thyroid gland is concerned, *MacCarty*, from a study of over 2500 thyroid glands removed at operation, divided these into the symmetric and the asymmetrical or nodular. The symmetrical glands contain various combinations of an adult and a fetal type of tissue element or of hypertrophied acini containing colloid, or of acini that contain little or no colloid material, but that possess lumina almost completely filled with large hypertrophic or hyperplastic cells. The simple nodular or simple symmetric thyroids contain nodules with a fetal type of cell, while the remainder of the parenchyma of the thyroid gland possesses various combinations of the tissue elements described under the symmetric thyroids. The complex nonsymmetrical thyroids may show, in addition, various combinations of the tissue-element types in the nodules.

Still more recent studies on the pathology of the thyroid gland have been made by *Wilson* and by *Plummer*, who base their conclusions on the enormous material of the Mayo Clinic. These authors divide goiters with symptoms of intoxication into, clinically, the exophthalmic and nonexophthalmic forms. In the first form only is there a true hypertrophy and hyperplasia of the gland tissue. The pathology of toxic nonexophthalmic goiter is one of increased parenchyma through regenerative changes in atrophic parenchyma, or the formation of new parenchyma of the fetal type with an increase in each instance of secretory activity and of absorption. The process is a chronic one, but one sufficiently active to cause the patient to consult a surgeon earlier than do the true exophthalmic goiter patients, in whom the disease is acute.

*Gilbride* has examined the thyroids in six cases of exophthalmic goiter bacteriologically, and isolated a bacterium in one case only—micrococcus tetragenes.

With regard to the treatment of Basedow's disease, internists and surgeons occupy hostile camps. More and more has the opinion gained ground that the condition is an affection demanding surgical attention. Nevertheless border-line cases should first be given the benefit of properly directed medicinal dietary and physiotherapeutic measures.

*S. Solis-Cohen* has a strong conviction that surgical measures are indicated only in a small minority of the cases of exophthalmic goiter that come under the eye of the alert physician. He recognizes the following indications for treatment.

1. When the disease has persisted and, despite proper medical and hygienic care, is advancing.
2. When the disease is progressive or far advanced.
3. When the patient's means or social status is such that rest is impracticable, and the disease, although slight, has persisted under treatment for a year or more without signs of yielding.

This author estimates the number of cases in which surgical intervention is necessary at about 5 per cent. of the total number. He recommends individualization in treatment, the keynote of which is rest. Correction of the eye conditions, fresh air, proper diet, the drinking of hot water for its diuretic and eliminative action, intestinal antiseptics, neutral quinine hydrobromide (5 gr. or more thrice daily), ergot, picrotoxin, calcium chloride, digitalis, strophanthus, and even cactus all have their place in the medicinal therapy. In addition hydrotherapeutic measures, electricity (ionic application of iodine to the gland or to the cervical sympathetic, or the high-frequency discharge to the neck or to the vertebra prominens) and the ice-bag or ice-coil to the heart or gland or spine. Among organic extracts the author recommends especially thymus extract (0.5–3 gm. per diem) or a combination of thymus gland with adrenalin.

*Falta* has in the text cited the fact that in many cases of Basedow's the thymus gland is enlarged. The use of thymus extract in Basedow's disease had better be dispensed with. The editor would advise against the employment of adrenalin on account of the tendency to glycosuria in Basedow's disease.

*Musser* summarizes the results of consideration of medical and surgical treatment in the dealing with goiter, especially exophthalmic goiter, as follows:

1. "Endemic goiter should not be treated surgically until proper general treatment has been employed for a long time.
2. Surgical intervention should not be advised in cases of goiter associated with functional or organic disturbances of other secretory organs until the associated disorders are removed or relieved.
3. If relapses occur in spite of general treatment, or in spite of treatment directed against the disorders of other organs, a goiter should then be treated surgically.
4. Medical treatment should be continued from six to twenty-four months. Favorable results should not be promised unless the patient is under the absolute control of a physician, so that treatment by rest, diet, bathing, physical therapy, and so forth may be carried out with precision and continuity.

5. Surgical intervention requires the same rigid and prolonged after-treatment to give permanent results."

*Musser* believes that the surgeon does too much, the internist too little, in the treatment of goiter.

*Abrams* recommends for exophthalmic goiter stimulation of the vagus nerve by direct percussion or concussion over the seventh cervical spine. In addition, he recommends pilocarpine, hypodermically or in doses of $\frac{1}{10}$ gr. three times daily by mouth. With regard to this treatment it may be said that *Abrams* uses it to give tone to the vagus nerve. If it is granted that this method of procedure really does stimulate the vagus nerve, the treatment is certainly not indicated in the so-called vagotonic forms of the disease.

*Stoney* reports forty-one cases of exophthalmic goiter (various types) treated by X-rays. (The anode is 6 in. from the skin, which is protected with four layers of blankets. One-half to 1 milliampere of current is run through the secondary.) Of the forty-one cases fourteen were completely cured, some of these remaining well for over two years after the treatments, twenty-two more have improved very much, four were somewhat better, only one did not do well. *Snow* in a discussion of *Stoney's* report stated that he had seen good results from the application of the static wave current, and from the use of *Abram's* percussion method.

*Lewi* reports a series of thirty-four cases of exophthalmic goiter and perverted thyroid secretion [?] that he treated with high-frequency currents, with results that he considers exceptionally good.

The editor believes that no harm is done by expectant treatment with high-frequency currents, combined with rest and other rational methods of physiotherapeutics; and that such currents might be used as an alternative for the X-rays, or as a substitute for them before they are used. Temporizing with such methods should not, however, supersede surgical procedures in appropriate cases. The use of radium is mentioned by *Marine* in a review, and *Turner* reports that results from local irradiation with radium were as favorable as those of the X-ray.

After hearing what these internists and physiotherapeutists have to say let us turn our attention to the surgical side of the question. According to *Mayo*, the early operation of ligation cures many cases. Early as well as advanced cases can be cured by partial thyroidectomy. The mortality in these cases will vary from 1 to 4 per cent. Combined operations are often indicated in bad cases: first ligating one or both superior vessel areas, and, later, doing a partial thyroidectomy.

Local anesthesia is indicated in most ligations. Local or combined or straight ether anesthesia are the methods used for thyroidectomies, according to the preference or experience of the individual operator.

In 900 operations performed on the thyroid in St. Mary's Hospital, Rochester, Minn., during the first ten months of 1911, the mortality was 1 per cent.

*Halsted* in his recent article on thymectomy as a surgical procedure in the treatment of Basedow's disease publishes the following instructive table, which he in turn has copied from *Klose* (Die Basedowsche Krankheit, Ergebn. d. inn. Med. u. Kinderh., Band X, 1913).

RESULTS OF OPERATIONS FOR BASEDOW'S DISEASE

| Year | Authors | No. of cases | Cures, per cent. | Considerable improvement, per cent. | Slight improvement, per cent. | No improvement, per cent. | Deaths, per cent. |
|---|---|---|---|---|---|---|---|
| 1896 | Schultz | 20 | 90.0 | ............ | ......... | 5.0 | 5.0 |
| 1898 | Wolf | 9 | ...... | 66.5 | ......... | ...... | 22.5 |
| 1900 | Helferich | 6 | 66.6 | 16.7 | ......... | ...... | ...... |
| 1900 | Reinbach (V. Mikulicz) | 18 | 66.5 | 22.5 | ......... | 5.5 | 5.5 |
| 1902 | Witmer (Krönlein) | 23 | 40.9 | 36.2 | 9.2 | 9.2 | 9.2 |
| 1902 | Th. Kocher | 59 | 76.0 | 14.0 | ......... | 3.3 | 6.7 |
| 1903 | Curtis | 11 | 60.0 | 10.0 | ......... | ...... | 30.0 |
| 1904 | Mayo | 40 | 67.5 | 17.5 | ......... | ...... | 15.0 |
| 1905 | Lessing (König) | 8 | 50.2 | ............ | 37.3 | ...... | 12.5 |
| 1905 | Hartley | 21 | 87.5 | ............ | ......... | ...... | 12.5 |
| 1906 | K. Schultze (Riedel) | 50 | 72.0 | 12.0 | ......... | 2.0 | 14.0 |
| 1907 | A. Kocher | 167 | 93.7 | ............ | ......... | ...... | 6.3 |
| 1907 | Itzina | 7 | 85.7 | ............ | ......... | 14.3 | ...... |
| 1907 | Mayo (only new cases) | 136 | 78.2 | 19.6 | ......... | ...... | 2.2 |
| 1907 | Landström | 54 | 50.2 | 15.3 | ......... | 29.0 | 5.5 |
| 1908 | Moses (Garrè) | 28 | 16.9 | 41.6 | 24.9 | 12.5 | 4.1 |
| 1908 | Klemm | 32 | 93.2 | ............ | 3.4 | 3.4 | ...... |
| 1908 | Th. Kocher | 153 | ...... | 98.7 | ......... | ...... | 1.3 |
| 1909 | MacCosh | 22 | 14.5 | 72.7 | 8.2 | 4.6 | 4.6 |
| 1909 | Hänel | 21 | 38.1 | 42.8 | ......... | ...... | ...... |
| 1911 | Sudeck | 26 | 84.6 | 4.0 | ......... | ...... | 4.0 |
| 1911 | Baruch | 40 | 72.5 | 12.5 | ......... | 15.0 | 15.8 |
| 1911 | v. Eiselsburg | 44 | 61.4 | 34.1 | ......... | 4.0 | ...... |
| 1911 | Enderlen | 40 | 70.0 | 20.0 | ......... | 2.2 | 2.2 |
| 1912 | Klose | 61 | 75.5 | 9.8 | ......... | 1.6 | 13.1 |
| 1912 | Weispfenning | 30 | 60.0 | 6.6 | ......... | 23.3 | 10.0 |

*Küttner* in a discussion tells of the results of his researches among old subjects of exophthalmic goiter, with results that speak immeasurably in favor of the surgical procedure. He stated that it was especially important to study the remote results of operation in cases of Basedow's disease, and that we should not consider of such vital importance merely the immediate results. Of twenty-one well-marked cases treated conservatively, none had recovered health, nine having been treated for a period of at least fifteen years, 35.7 per cent. had died, and only one was able to work. Of the cases of the same series that were operated on only 17.3 per cent. had died, and of those living, 86.2 per cent. had either entirely recovered or were able to do their work.

*Halsted* himself has done about 650 operations in 500 patients with Basedow's disease. A one-sided lobectomy resulted in an approximate cure in possibly 60 per cent. of the cases. For scientific purposes, to ascertain the rôle of the thymus in Basedow's disease he recommends primary thymectomy, or secondary thymectomy where both lobes of the thyroid have been removed without proper effect. He states, however, that he is sorely tempted to remove a portion of an enlarged thymus when he meets with it in the course of an operation for Basedow's disease.

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# CHAPTER III

## THE CRETINIC DEGENERATION

The enormous social significance of the cretinic degeneration in the countries affected by it may be seen by the glimpse of the following figures, which I take for the most part from the works of *Ewald* and *E. Bircher.* In Switzerland 7.2 per cent. of the applicants for military service must be rejected on account of goiter, and 2 per cent. must later be discharged. In Cisleithania there occurred for every 100,000 inhabitants 71 cretins; in many strongly infested districts, for example, in Murrau, in the Steiermark, there are more than 1000 cretins per 100,000 inhabitants. In France, in 1873, there were about 1 per cent. goitrous among the inhabitants and 0.3 per cent. cretins and idiots; in Piedmont in 1883 about 0.15 per cent. of cretins; in Lombardy 0.2 per cent., etc. The etiology of this affection is not as yet explained. The study of the geographical distribution shows that goiter, goiter heart, endemic cretinism, and endemic mutism belong together. Typical Basedow's disease is rare in goitrous districts. Manifestations of hyperthyrosis are commonly found there combined with those of goiter heart. The parallelism in the distribution of endemic mutism with that of endemic cretinism are convincingly shown by the investigations of *Bircher* for Switzerland and the statistics of *v. Wagner* for Austria. For lower France there are the observations of *Lobenhoffer.* The group relationship of goiter and endemic cretinism is not only seen in the fact that the cretins are almost always goiter carriers, but also through the almost unexceptional occurrence of goiters in the ancestry of the cretins. This and other established facts point to a common etiological factor in the different forms of the cretinic degeneration. As to this all observers agree. On the contrary, there is as yet no agreement as to the question whether the manifold manifestations of the cretinic degeneration are called into existence only by the mediation of the strumous degeneration of the thyroid gland, or a part of these are directly produced by the strumous noxus and thus are coordinate with the struma.

The cretinic degeneration is found in Europe especially in the central Alps; large goitrous districts exist in addition in the Carpathians, the German middle mountains, and the Pyrenees. Also in the other parts of the earth the goiter districts lie in mountainous districts. The goiter districts change; localities that were formerly infested become goiter-free, and conversely. Sometimes there occurs an epidemiform breaking out. When the affection retrogresses in one district, first the most severe forms of the cretinic degeneration disappear for the most part, while the goiter alone remains for some time (for example, in Baden and Thüringen). Persons who come from a non-goiter neighborhood into a goiter neighborhood often develop goiter, or become affected with it after their return. *E. Bircher* here cites an instructive example. A family in a non-goiter neighborhood had healthy children. When they came into a goiter district, the parents themselves remained non-goitrous but had a cretin for a child. *Kocher* reports another example: The parents were healthy, and as long as they lived in a goiter-free district had nine healthy children. When they came into a goiter district, they had three cretin children of which the first was the most pronouncedly affected. Again the thirteenth child was normal, but very small. *Breitner* has recently published a similarly instructive case. Enormous outbreaks of goiter have been often observed in regiments after their stationing in goiter districts. Families that remove from goiter districts can soon lose their goiters. Also the occurrence of goiters is not rarely observed in animals, after their transference to a goiter district.

The noxus of goiter is bound in the drinking water. In the goiter territories there exist indeed especial goiter brooks; there are numerous examples in the literature of goitrous communities becoming free of goiter after they had established drinking-water conduits from goiter-free vicinities.

The occurrence of the goiter noxus in the water is bound together with a definite geological structure of the soil. This view has been especially promulgated by *Bircher, Jr.*, on the ground of his penetrating studies and excellent observations. According to *Bircher*, cretinic degeneration is found only upon the marine deposits of the paleozoic ages, the dryassic and the tertiary ages, while the eruptive formations, the jurassic and fresh-water deposits, are free from the noxus. This view is not generally shared, but is, however, set upon a working basis by the works of *Johannesen* and latterly by *Bircher, Jr.*, and *Lobenhofer*. The practical significance of the investigations of *Bircher, Sr.*, is seen at its best in that the community Rupperswill has become goiter-free since it has led its water from springs lying in jurassic deposits. A like example is furnished by the village Asp.

Previously healthy animals may become goitrous on having goiter water furnished to them. The noxus goiter goes through a Berkefeld filter; it is destroyed by temperature higher than 70° C. (*E. Bircher*). Therefore it is likely, as *Wilms* first assumed, that the noxus is not a miasma, but a toxin or toxalbumin from an organic substance.

It does not dialyze, therefore behaving like a colloidal emulsion. The struma produced shows histologically changes that are degenerative, and on the use of weaker goiter water, also hyperplastic. The animals developed cardiac hypertrophy, and many remained behind in growth.

### 1. Goiter

We understood by this term a *noninflammatory, diseased alteration of the thyroid, mostly associated with enlargement of this gland, while the thyroid in* *most cases shows hyperplastic manifestations, and always degenerative manifestations.* The hyperplasia may affect the parenchyma as well as the vessels. The degenerative nature of the alteration is seen in the fact that the hyperplasia of the parenchyma is for the most part unaccompanied with increase in function. Therefore either the parenchyma must be less capable of functionating or the giving off of secretion is hindered by sclerotic process. For the most part there is found sufficient parenchyma capable of functionating. According to the stronger or weaker participation of the hyperplastic or degenerative processes we distinguish parenchymatous, vascular, or fibrous—further, diffuse or circumscribed—goiters; when the stagnation of the secretion is greater, we have colloid or cystic goiters. In goiter neighborhoods there also occur hyperplastic congenital goiters. There seems to exist a certain relationship between goiter and myomata of the uterus. At least it has been observed that in strumous women, who also suffer with myomata, the struma also decreases in size with the retrogression of the myoma at the menopause (*Ullmann*). Concerning the further distinctions, the differential diagnosis, and the surgical treatment, I shall refer [the reader] to *v. Eiselsberg's* monograph. Among the *non-surgical methods of treatment,* I mention only the iodine treatment. This is the more effective the more the hyperplastic alterations and the less the degenerative alterations are present. That in certain neighborhoods iodine therapy often leads to manifestations of hyperthyrosis has already been mentioned in detail in the chapter on Basedow's disease. The thyroid therapy recommended by *v. Bruns* is less used nowadays. Not much can be expected from the treatment of ordinary goiter by the X-rays.

## 2. Goiter Heart

The coincidence of goiter and cardiac disturbance is very common. The statistics of *Schranz,* which are based on an investigation of two hundred and sixty-four goitrous school children, one hundred and seventeen goitrous adults, and seven hundred and twenty autopsy protocols of the Innsbruck Pathologico-anatomical Institute, show that after subtraction of the valvular defects, 23 per cent. of the children and 49 per cent. of the adults suffered from heart trouble. Of the autopsied cases one hundred and eighty-eight showed degenerative alterations of the cardiac muscle, some with hypertrophy. While these figures can only partially stand ground against criticism (*Wölfler, Fr. Kraus, Minnich*) they are indeed, even when reduced, sufficient to show the common coincidence of goiter and cardiac disturbances. *Rose* showed, before *Schranz,* that the stagnation [congestion] in the lesser circulation caused by the large goiter can lead to dilatation and insufficiency of the right heart (so-called *Rose's* goiter heart). When the embarrassment to respiration on account of the goiter enters more into the foreground we call the condition, following the lead of *Kocher, pneumonic* goiter heart. Conversely, primary stagnation in the lesser circulation may lead to enlargement of the thyroid gland with greater or less manifestations of hyperthyroidism (*Revilloid's* "goître cardiaque").

*Revilloid* already mentioned that slight manifestations of hyperthyroidism may occur with this "goître cardiaque." This was later made intelligible through the experiments of *Blum*, which followed, that ligation of the thyroid veins leads to an eddying out of the thyroid-gland secretion and therewith to a slight hyperthyrosis. Later, cirrhotic changes occur in such thyroids.

*Fr. Kraus* first mentioned that there were numerous cases of cardiac disturbances in goiter in which all stagnation is absent and in which, therefore, the mechanical factor as a cause does not come into consideration. In the *light* forms of these are found tachycardia, often dicrotism of the pulse, slight strengthening of the apex impulse, beating of the carotids, sometimes arrhythmia, glittering eye, sometimes indeed a slight degree of exophthalmus, inclination to sweating, trembling, and eventually slight heightening of the fundamental exchange, in short phenomena of a slight hyperthyrosis. In the *severer* forms are found, in addition, hypertrophy and dilatation of the heart and degenerative changes in the cardiac muscle. Also *v. Mukulicz* and *Reinbach* found similar symptoms in a great percentage of the goitrous that were examined by them.

The fact that hypertrophy and premature degeneration of the cardiac muscle is found so frequently in the goitrous with cardiac disturbances indicates that we are here not dealing with the ordinary forms of hyperthyroidism. *Fr. Kraus* first championed the greater nosological independence of this form; the newer investigation results of *Minnich* and *E. Bircher* seem fully to corroborate his contention. The opinions of *Minnich*, in his significant monograph, in so far as he regards these Basedow's manifestations as the expression of a diminished thyroid-gland function, are not shared by the author. Entirely new views, however, are opened by *Minnich* in his description of cardiac disturbances in relatively young strumous individuals of both sexes, which mostly set in with new impulses in the growth of the goiter and lead objectively to enlargement of the heart, eventually with the gradual development of a protrusion of the precordium, and frequently also of accidental murmurs and subjectively to pains in the cardiac region, pricking pains, pressure, painful precordial points of tenderness, and cardiac palpitations. Such cases may remain stationary a long time, or even become cured, or they may go over into tachycardia. This was the case in eleven of twenty cases. Here, therefore, we are dealing with a form of goiter heart in which, at least in the beginning, hyperthyroidal symptoms were hardly present.

The fundamental significance of these observations is supported by the experiments of *E. Bircher*. *Bircher* saw enlargement of the heart almost regularly in the animals in which he artificially induced struma by giving them goiter water to drink. The weight of these hearts averaged one-third more than that of the hearts of the control animals. The heart muscle microscopically for the most part showed degenerative changes. *Bircher* refers the cardiac damage directly to the goiter noxus and in agreement with *Minnich* sees in it a disease sui generis.

According to a personal communication from *Prof. Scholz* also the endemic cretins usually have bad hearts, but no hypertrophy; this may hang together with the gradually and long-continued action of the goiter noxus, perhaps also with the slight "expressions of life" [Lebensäusserungen] of such individuals.

### 3. Endemic Cretinism

**Symptomatology.**—The *habitus* of endemic cretinism shows a much greater multiformity than that of sporadic cretinism. *Diederle* compares the photographs of seven youthful cretins of eighteen years of age from Bern with that of sporadic cretins from fourteen months to twenty-one years of age, and shows that despite the fact that the latter come from different countries, they show much similarity to one another, while the others resemble one another less strongly although they come from the same family. *Diederle* cites the doctrine of *Maffeis*, that there is no cretinic prototype. Also the skulls in endemic cretinism show greater differences; in many the skull is small, the forehead low and receding; in others the skull is abnormally large. Regularly the root of the nose is retracted, although never to so great a degree as in chondrodystrophy; for the most part the eyes stand wide apart, the throat is short and thick, the lips are cushiony, the facial expression morose. Ordinarily the skeleton shows abnormalities—ankyloses, scolioses, etc. *Scholz* describes flattening of the head of the femur. The pelvis is often narrowed in all dimensions, and the bones are provided with swellings [Wülsten]. Also there is difference in the degree of dwarfism. *v. Wagner* observed individuals under 90 cm., although there are full cretins over 150 cm. in body length. *E. Bircher* of Aarau has kindly provided me with Figs. 18–22. Fig. 18 shows the multiformity of the facial expression and the shape of the skull in endemic cretinism.

The duration of life of the cretins is in most cases shortened, yet some cretins attain a very high age. *Kocher* reports about seventy-year-old and even one-hundred-year-old cretins.

The figure is plump, the gait inelastic, the muscles are poorly developed; individuals with completely developed forms can indeed not walk, but only creep. This depends, however, not as much on the muscular weakness as on the want of every fine coordination. The *skin* of the face is often very lax, numerous transverse wrinkles traverse the forehead and lend to the face an old appearance. The development of the myxedema is very diverse. *Magnus-Levy* and *v. Wagner* found in many cases typical supraclavicular pseudolipomata, and also on other places of the skin very evident pad-like swelling and myxedematous alteration of the mucous membrane. *Scholz* found the skin only atrophic. In 60 per cent. of the cases investigated by *E. Bircher* the myxedematous swelling of the skin was absent. There are also cases that sweat profusely. The hairs are for the most part short and bristly, the nails torn, the teeth defective, the hair in the axillæ and on the pubes may be absent or only sparsely developed. Umbilical hernia in children as well as obstipation and distention of the abdomen is just as frequent as in sporadic cretinism. Often conjunctivitides are found, and as a result of these, eczema of the palpebral borders. According to *Hitschmann*, the conjunctivitides probably develop through disturbance in the leading off of the tears on account of the saddle nose. There mostly occurs a fairly high degree of anemia. The *disturbances of intelligence* of the cretins may vary from the slight grades of feeble-mindedness up through all the grades to the failure of all mental expression—the so-called plant man. In such cases all development of speech is also absent. In most cases, however, some psychical development is still present. The perception, however, is somewhat

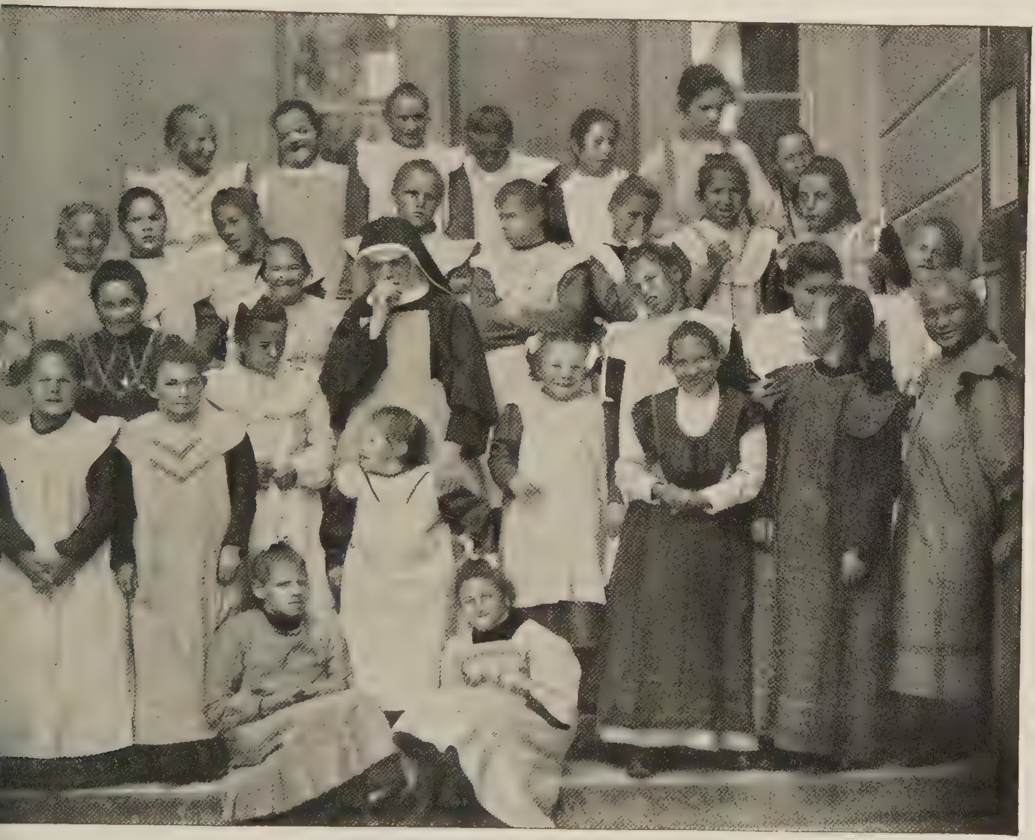

FIG. 18.—Group of endemic cretins from Aarau.

slowed, the memory very poor; as for the emotions, the cretins show a certain clinging for the persons who feed them or hate against those whom they regard as enemies.

The pathologico-anatomical findings in the *brains* of *cretins* are very diverse. Often they are only trivial; in most cases, however, there are found several alterations, and these of greater intensity. *Scholz* and *Zingerle* found at times chronic meningitic alterations and a slight grade of hydrocephalus. The brain may be smaller in toto—or in individual lobes; often it is highly asymmetric, sometimes there is found a persistence of the juvenile developmental stages, or in rare cases excessive development of the brain. The disturbances of development may affect the hemispheres as well as the brain-stem, the cerebellum, etc. The confirmation of the surface of the brain is often pathologically affected in that the convolutions are smaller or their number lessened. In abnormally small brains of cretins it may well be supposed that the smallness of the brain is primary, that of the skull secondary;

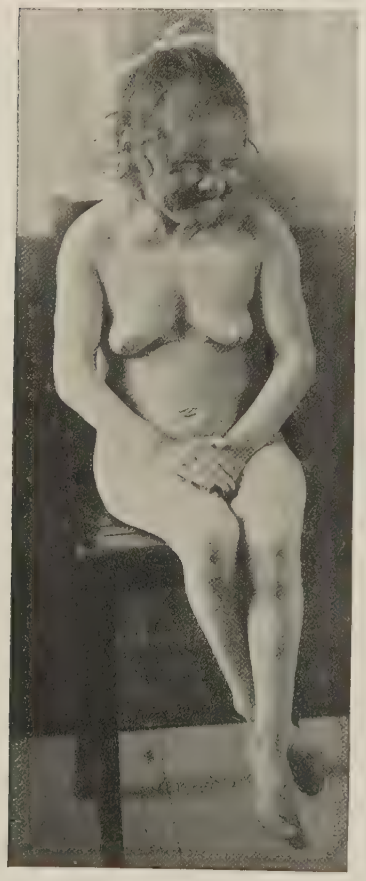

FIG. 19.—Endemic cretinism.

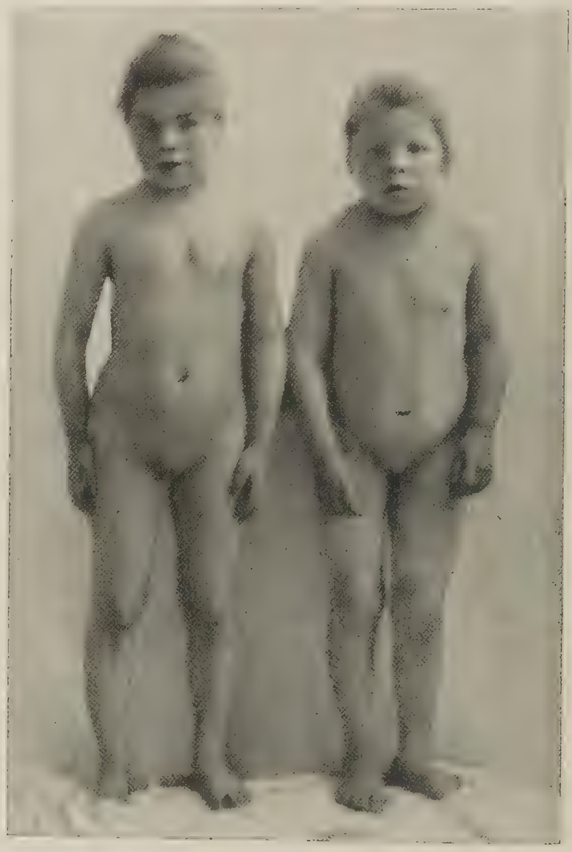

FIG. 20.—Cretins with myxedematous facial expression.

as *Bourneville* taught of idiots' brains. The brain substance of cretins, according to *Scholz* and *Zingerle*, is often strikingly compact, the amount of gray matter [relatively] exceeding in mass the white.[1] The disturbances of development may affect different parts in very different ways. The inhibition of the development of the sense organs is certainly to be ascribed, in part, to the faulty development of the central organs.

*The nervous status* commonly shows increase of the reflexes, according to *Scholz* in 52 per cent.; the field of vision was found by *Ottolenghi* to be restricted, especially outward and upward. *Hitschmann* found the eye grounds normal in nearly all his cases; only in certain cases were crescents directed downward found, whose relationship with the cretinic degeneration was entirely obscure. The testing of sensibility, of the sense of taste and smell, naturally presents great difficulties.

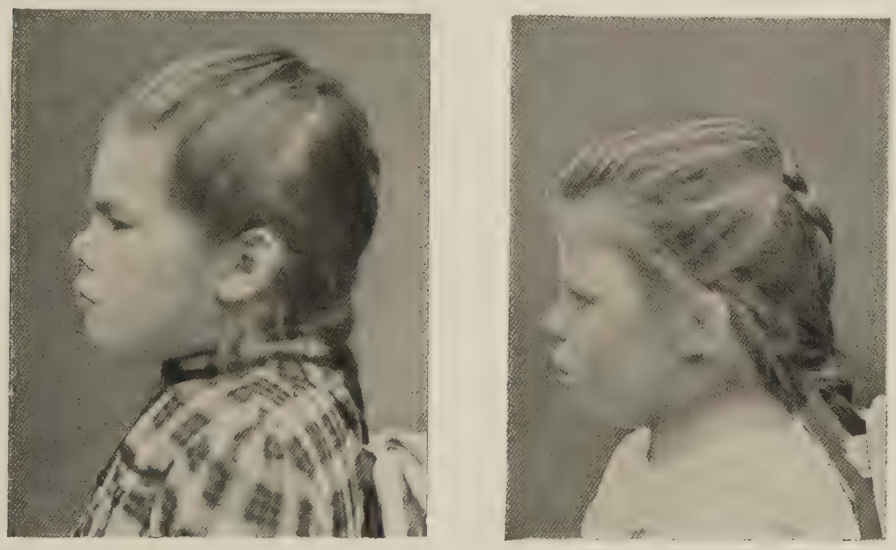

FIG. 21. FIG. 22.

FIGS. 21 AND 22.—Cretins with myxedematous facial expression.

The *disturbances of hearing* are of very diverse degrees. In many cases, the power of hearing is fully intact. In others, there exists a slight or severe grade of hardness-of-hearing or mutism. Frightfully large is the number of completely deaf-mutes.

**Endemic Mutism.**—In all countries in which cretinism is endemic there is found a large number of deaf-mutes. According to the older statements of *St. Lager*, Switzerland possesses five thousand cretins and four thousand deaf-mutes. To the latter, of course, belong a part of sporadic mutism, that is, what depends on a meningitis in earliest youth, on otitides or formation anomalies of the brain, that have nothing to do with the goiter noxus. A very great number, however, belong to endemic cretinism (according to *E. Bircher*, 80 per cent. in Switzerland). Also in Austria, and especially in the Stiermark, are found an enormous number of deaf-mutes. *Scholz* found among the cretins examined by him 29 per cent. deaf-mutes and 32 per cent. hard-of-hearing. The intensity of the disturbance of hearing does not go parallel throughout with that of the remaining cretinic symptoms. There are complete cretins that show only slight disturbances of hearing and speech. In others the mutism may be the chief symptom of the cretinic degeneration (larval form of *v. Eiselsberg*).

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[1] I have here rectified the author's error by reference to *Scholz* and *Zingerle's* article. The German text here transposes "white" and "gray".—*Editor.*

The statements as to the functional disturbances or the pathologico-anatomical findings in the deaf cretins and in the endemic deaf-mutes diverge greatly. *Hammerschlag*, whom we have to thank for the first exact investigations, found on the one hand alterations in the peripheral hearing apparatus, and on the other only disturbance of the perception of sound, as also found *Scholz*, *Fröschel* and *others*. Further there was found in endemic cretinism incomplete ossification of the stapes, inhibition of development of the epithelial cells in the ductus cochlearis (*Habermann*, *Alexander*), shortening of the base of the skull and thereby disturbance in the development of the organ of hearing (*Danzinger*, *Bircher*), incomplete ossification of the organ of hearing with hyperostotic growths at other places (*Moos* and *Steinbrügge*). Anomalies of the malleus (*Nager*), myxedematous thickening of the tympanic mucous membrane, etc., have been regarded as the cause of the hardness-of-hearing. Recently, *E. Bircher* has strenuously criticised a portion of these findings or their significance. To-day we may safely assume that we may ascribe great importance to the degeneration in the cortical centers or the developmental inhibitions in the cortical centers, and that the different alterations are directly elicited by the goiter noxus and are coordinated with an insufficiency of the thyroid that finally sets in (*Pineles*).

The inhibition of the *development of speech* in endemic cretinism is extraordinarily different [in degree]; where hearing is entirely absent, of course, the development of speech is also absent. We do, however, see cases in which in spite of high-grade disturbances of hearing only relatively slight defects of intelligence are present. Of course, in these cases articulation is poor (*Hammerschlag*). In other cases, in spite of good hearing, intelligence and the development of speech are minimal. Here also do we assume a developmental inhibition of cortical centers (*Scholz* and *Zingerle*). Where the endemic shows less intensity, defects of intelligence may be entirely absent (*H. Bircher*).

Investigations as to the metabolism in endemic cretins have been published only by *Scholz*. *Scholz* designates the metabolism as very sluggish. The amounts of urine were very slight, as well as the exchange of albumin and of salts. The excretion of nitrogen, uric acid, creatinin, and sodium chloride was very slight, and that of urea, the xanthin bases, ammonia, and sulphuric acid showed corresponding proportions. There was further noted a tendency to retention of phosphorus and nitrogen. The metabolism therefore shows a relation analogous to that in myxedema.[1] Very interesting are the results of feeding with thyroid gland. Diuresis increases. The nitrogen elimination was not, however, essentially influenced, while the body weight diminished. Therefore chiefly nitrogen-free substances must be consumed.

As the cretins investigated showed no distinct myxedematous swellings, it was not to have been expected that the initial increase of the albumin combustion observed in myxedema would be present. *The experiments all show that the depressed albumin exchange in endemic cretinism cannot be stimulated so easily as in myxedema.* I cannot see in this an analogy to Basedow's disease, as *Scholz* does, as the absence of a further increase of nitrogen elimination through thyroid substance in Basedow's disease may have its ground in the circumstance that the excess of thyroid-gland secretion does not come distinctly into action, if in higher grades of hyperthyrosis the energy of the albumin decomposition has reached a great intensity. *Scholz* further observed in his experiments that under the influence of administration of thyroid gland, the calcium in the urine decreases markedly and increases in the feces, as we have also observed in normal individuals.[2]

For the most part there is found in cretins a fairly evident hypoplasia of the *genitalia*. In women the labia and the uterus are mostly small, but it may happen that the external genitalia are relatively well developed; the ovaries are small and often show small, cystic degeneration; the menses are absent or are scanty and irregular; the mammæ are poorly developed and without glandular tissue. In men the penis is often very small, the testicles are not well descended, and on microscopical examination show spermatozoa very sparingly. The scrotum is lax. In both sexes the secondary sexual characters are for the most part very defectively developed; the sexual instinct is entirely absent or is very weak only; in many a light case, however, procreative power and conception are observed. *E. Bircher* reports concerning a cretin of the most severe grade who conceived; the fetuses, however, are not capable of living, even when, as in a case of *Eppinger*, they show no sign of cretinic degeneration. The genitalia can, however, like ossification, still show a late development.

Worthy of observation are *Schönemann's* investigations, which show that in neighborhoods where goiter is endemic very commonly strumous alterations are found in the glandular part of the *hypophysis*. Among one hundred twelve cases, the hypophysis was normal in only twenty-seven. These persons also did not have a goiter. Among the cases with goiter, there was only one in whom was found a hypophysis that could be regarded as probably normal. "In persons with struma of the thyroid, there was always found enlargement of the hypophysis, and indeed either proliferation of the connective stroma, also chromophilic strumas, strumas with especially vascular development of the stroma and hyaline degeneration and swelling up of the columns of cells, and finally those with marked colloid formation." Also *v. Cyon* found strumous alterations of the hypophysis very frequently in Bernese dogs. *The goiter poison therefore works deleteriously on the hypophysis.*

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[1] "Not however to experimental athyrosis proper." This statement of *Scholz* is unintelligible to me, as according to my knowledge, an essential difference between the metabolism of myxedema and that of cachexia thyreopriva does not exist.

[2] See the chapter on hyperthyroidism.

As in sporadic cretinism, the *disturbance in bone-growth* consists of delay in the epiphysial closures and in retarded appearance of the bone-nuclei. *Langhans* first described, in the skeletons of five cretins, the remaining behind in the ossification and commented that also the cretinoids show a similar, although less marked, remaining behind. "The bones previously laid out in cartilage grow slowly in their length; the epiphyses remain low, the boundaries of ossification progress very slowly, the nuclei of ossification in the epiphyses occur very late, and the epiphysial discs are retained for long beyond the normal term. Remnants of these discs are still to be found in the forty-fifth year." *v. Wyss* has confirmed the observations of *Langhans* by means of the X-ray examination of numerous cretins and cretinoids—and incidentally has finally contradicted the previous view that in cretins premature ossification of the epiphysial junctures occurs. This delay in the epiphysial closure makes, as *v. Wyss* emphasizes, intelligible the former observations of *v. Wagner* that in endemic cretins, even in late life, the growth in height may go on. To this extent the disturbance in the ossification agrees fully with that in sporadic cretinism, although on the other hand there are differences that are important from the point of view of differential diagnosis. Already *v. Wyss* pointed out that the retardation in the ossification for the most part lasts only a few years, so that only rarely are the epiphysial junctures found to be open after the twenty-fifth year.

*Diederle* mentions especially the extensive difference from thyroaplasia in this behavior of the epiphysial junctures, which in thyroaplasia, if thyroid therapy be not introduced, often remain open. In youthful age in endemic cretinism, however, the remaining of the ossification behind that of the normal individual is not inappreciable. *Diederle* publishes a very instructive table in which he compares the ages of the cretins of *v. Wyss* as estimated from the radiograms of the hands with the actual ages of the individuals. He finds in eleven cretins between the ages of seven and eighteen years a remaining behind of ossification of from three to seven years. *Breus* and *Kolisko* state moreover that in six of the cretin skeletons examined by them never did all the epiphysial junctures remain open until an advanced age, therefore *there did not exist in all bones the same* degree of disturbance of growth, and that there resulted from this a *disproportioned skeleton;* the extremities are slender but shortened near the trunk, and there exists in this respect a difference between the cretinic dwarfism and the true dwarf described by *A. Paltauf*, in which all epiphysial closures remain behind, in like manner, as in a former child stage of development. In those cases of endemic cretinism in which the epiphysial closures are already ossified, thyroid therapy can naturally no longer lead to growth in height.

*E. Bircher* has recently studied the disturbances in growth in endemic cretinism in a large amount of material (fifty-six cases) and has come to the same results as *Breus* and *Kolisko*. The inhibition of the ossification affects only the age of development. After thirty years of life the epiphyses and synchondrosis were found open only exceptionally. Also *Bircher* found throughout that the inhibition in the individual bones is quite dissimilar and led to a disproportioned skeleton. Not rarely *E. Bircher* found a coxa vara or a humerus varus.

Of quite a manifold nature are the findings as to the *teeth* of cretins. *Kranz* examined thirty cretins from the Knittelfeld Institute in Steiermark as to jaw and tooth formation, and found numerous anomalies of the jaws, retarded teething, besides factors that give occasion to anomalies of the position of the teeth. Further he commonly found alterations of the structure, defects of the enamel, hypoplasias and erosions and very frequently caries. That these anomalies were not produced by the experimental extirpation of the thyroid gland in animals is made intelligible by the conception that athyrosis or hypothyrosis and endemic cretins are different conditions.

Very frequently statements are made that endemic cretins are *anemic;* with this agrees the fact that *Langhans* found in a grown cretin much fat marrow and little functioning marrow in the long bones. I was unable to find statements as to the leucocytic formula in endemic cretinism. *McCarisson*, however, reports on the basis of over one hundred blood examinations in endemic goiter a regular increase of lymphocytes and also mostly hypereosinophilia.

The statements as to the *thyroid gland* in endemic cretins vary greatly. *v. Wagner* found not a single normal thyroid in inspection of the neck of two hundred cretins. Very commonly the thyroid is not palpable, but very little value can be ascribed to this statement. In the most cases are found goitrous degeneration with atrophy. *DeCoulon* found in the thyroid gland of five cretins, who died at the age of twenty-six to thirty years, very little normal thyroid-gland parenchyma. One of these cases was fairly well developed mentally. *Hanau* examined three thyroid glands that all were small and showed a marked disappearance of the parenchyma. Also *Bayon* and *Getzowa* found high-grade degenerative processes, marked diminution of the functionating parenchyma, and enormous development of hyaline-degenerated connective tissue. *Getzowa* found, however, similar alterations also in the thyroids of idiots and microcephalics who did not show dwarfism. On the other hand, *Bircher, Sr.*, found abundant normal thyroid-gland tissue in the thyroid gland of one of the cretins that he operated on. Recently *E. Bircher* reports on the examination of over sixty cretins' thyroids, obtained on autopsy or on operation. Degenerative processes were present in all, but were of extremely varying intensity, which often did not run parallel with the intensity of the affection. In all thyroids moreover were found large portions of normal thyroid-gland tissue. *E. Bircher* found similar conditions in a series of endemic deaf-mutes. *Accordingly there were found in almost all cases sclerotic and atrophic processes, but in addition also always some functionating parenchyma.* Moreover there was hence no struma whose histological picture was characteristic for cretinism. *v. Werdt* arrives at the same conclusion on the ground of the examination of five strumas that histologically showed entirely the picture of a cretin's thyroid, without there being any sign of cretinism whatsoever in the actual case.

No essential alterations have as yet been found in the *parathyroid glands* in cretinism (*Scholz, Getzowa, E. Bircher*).

**Treatment.**—Before I consider the question as to the rôle that thyroid insufficiency plays in endemic cretinism, I should like to speak about the results of thyroid therapy. There are in the literature very contradictory statements as to this. *v. Wagner* saw very good results. They consisted in the disappearance of the myxedematous swellings, in the rapid development of the genitalia that had remained behind, in the diminution in size of the enlarged tongue, and even in the disappearance of an umbilical hernia, in falling out of the bristly hair and development of new hair of normal texture, in acceleration of dentition, before all, however, in the diminution in size of the fontanelles that had remained open, in the acceleration of ossification and in increase in height. The least satisfactory were its results on the psyche; it is true that there was usually a decrease in the apathy and in the lack of movements, yet the increase in the intellectual capability was usually very slight.

*v. Wagner* lays especial stress on the earliest possible beginning of the therapy. He also saw good results in individual cases from administration of small doses of iodine (through stimulation of the activity of the thyroid gland?). Still better results were obtained by *Magnus-Levy* in fourteen individuals from three neighboring villages from upper Münstertal in the Vosges. These individuals came from seven families. The cretinism had appeared in this neighborhood only a short time previously; goiters were usually present in the relatives, and also the parents showed symptoms of slight goitrous degeneration. In the individuals themselves the thyroid was in many cases not palpable, only in a few goitrously degenerated. The majority showed fairly well pronounced myxedematous symptoms. In the severest cases were present lordosis and pendulous abdomen, in all constipation and faulty development of the genitalia. One case was highly deaf.

It is further worthy of note that a case that had developed fairly normally up to the tenth year first showed signs of cretinic degeneration at the close of an attack of pertussis, and finally in the sixteenth year showed a rapid deterioration with distinct signs of myxedema; in none of the cases did there exist complete dementia. In all these cases there was a distinct improvement already, four to six weeks after the institution of thyroid therapy. After one and one-half years only one case showed an increase in height as low as 4 cm.—all the rest 11-17 cm. The myxedematous manifestations disappeared, and the intellectual ability improved considerably. Also *v. Eysselt* saw good results in forty-six cretins in the Littauer Amtbezirke [official district] in Mähren. In two the development of the genitalia was especially influenced. Also *Sofer* saw favorable influencing of the growth and in addition also a severe loss in weight. In two later communications *v. Wagner* reports about numerous cases that were treated with very good results. Also in these communications *v. Wagner* points out that the results were more favorable the sooner the treatment was begun. In certain light cases a cure may be obtained which persists even after withdrawal of the therapy. But also even when the therapy is begun in late life can entirely good results be obtained. In the severer grades of cretinism the result was indeed not so satisfactory.

Also the hardness-of-hearing may become essentially improved. In many cases of hardness-of-hearing, however, an improvement is but little accessible.

According to *v. Wagner*, cretinism for the most part is not congenital, but in the great majority of cases signs of cretinism first make their appearance in the first years of life. For an early diagnosis are important, first of all, the absence of disturbances of gait and speech, then the pale color of the face, the swellings of the skin, the apathy, the retardation of the closure of the fontanelles and the dentition, the gradual retraction of the root of the nose and the remaining behind in growth. In such cases of acquired cretinism a much better result of thyroid may be expected.

As an especially pretty example of the increase in height, I shall quote the following case of *v. Wagner:* A fifteen-year-old boy is 105 cm. tall at the beginning of the treatment; after a four years' treatment he has grown about 43 cm. that is about 29 cm. more than corresponds to the average growth at this period of life. Also the typical saddle-nose and the apathy have disappeared, he articulates fairly well, the hearing has improved, etc. On the contrary, cases in which the cretinism appears so early that we must assume a congenital cretinism are for the most part fairly refractory. In these cases an influencing of the disturbances of speech and intelligence is completely absent. But also in such cases a result seems possible when the treatment is instituted a short time after birth. Those cases of *v. Wagner* which after an initial normal development first remained behind in body and mental development after an infectious disease could indeed in part also be classified with sporadic cretinism.

On a still larger material is based the report of *v. Kutschera* as to the treatment of endemic cretinism in the Stiermark at the cost of the state. The treatment was given to one thousand eleven cretins; of these a great number was treated for only a short time on account of the insufficient interest of the parents and could not be considered in the judgment of the result. Also there were found numerous individuals who could not be considered as cretins and who were separated out at a later sifting. Only in 2.4 per cent. of all treated were the tablets not borne well. High-grade idiots and cases of pure mutism were rejected. Of great interest were the cases the growth of which could be followed for a long time. They were four hundred forty in number, of which only 10.2 per cent. showed only a less growth than corresponded with the age of life, 4.1 per cent. showed a growth corresponding with this age; 85.7 per cent., however, a growth that exceeded the normal at that age. Especially in the first years of life was the increase in height very significant, but also it occurred in those individuals at the beginning of the third decade in which, under normal conditions, growth ceases. As to the total results, which also took into consideration other cretinic symptoms, among six hundred seventy-seven cases there was an appreciable improvement in 42.8 per cent., a distinct improvement in 48.6 per cent., and in 8.6 per cent. no improvement at all.

Also *v. Kutschera* reports on light, previously treated cases, in which complete cure was obtained after a relatively short treatment.

In rather sharp opposition to these good results are the bad results of *Scholz* and also of *Lombroso*. The bad results of *Lombroso* are concerned with old cretins. *Scholz* reports concerning a very large number of cases. *Scholz* treated with thyroid tablets one hundred cretinous children in the infirmary at Knittenfeld. He began with one tablet and gradually increased to three tablets, and in certain cases up to eight tablets, per diem. The results throughout were unfavorable. The body weights quickly sank (in certain cases as much as 36 per cent.). The children became extremely weak, even bed-ridden, the appetite diminished, vomiting and diarrhéa occurred, apathy increased; three children died. Increase in height was not observed. Also there were observed other symptoms of hyperthyroidism, such as tachycardia, sweats, etc. *v. Wagner* believes that these unfavorable results of *Scholz* depend on too high dosage. *v. Wagner* and *v. Kutschera* gave only a half-tablet to small children and gradually increased to one tablet. Also older individuals were mostly given only one tablet a day. *Scholz* began with one tablet and increased apparently rather quickly to three tablets, in certain cases even higher. In my cases of sporadic cretinism, however, even much larger doses were necessary over even a longer time before the first manifestations of hyperthyroidism manifested themselves. *Scholz* later stated that he could not obtain any good results with small doses. Also *v. Wagner* stated that many severe cases, especially those which he regards as congenital cretinism, are either fully refractory, or that at least certain symptoms, especially the disturbances of intelligence and speech, can remain uninfluenced. The hypothesis that in such cases, in which the noxus has already done harm at a former period, already definitive irreparable damage has been done, especially in the central nervous system, can explain only a slight result, but not the complete failure of the thyroid-gland treatment, as these conditions also obtain in sporadic cretinism, and here thyroid-gland therapy is never entirely without [good] results.

We now take up the question as to what rôle the disease of the thyroid plays in endemic cretinism.

**Pathogenesis.**—*Kocher* and *v. Wagner* identify sporadic and endemic cretinism in that they refer all manifestations to a damaging of the thyroid gland. *Bircher*, *Ewald*, and *Scholz* ascribe to the arthyrosis component only a certain signification, and see in it only one manifestation of cretinic degeneration which is coordinated with other derangements.

I would like to summarize the factors that speak against the hypothesis of a thyroid disturbance alone, as follows:

1. *The action of thyroid therapy is not so constant as in sporadic cretinism.*
2. *The myxedematous symptoms are wanting in many cases or are only very slightly expressed.*
3. *The forms of the clinical manifestations of endemic cretinism are much more manifold.* To it belong the frequent association with mutism, further the occurrence of mutism in cases that otherwise show only few signs of cretinic degeneration, the incongruence between the inhibition of the mental disturbances and the other signs of the cretinic degeneration; cases that on the one hand show struma and rather high-grade disturbance of growth are, however, well developed mentally; on the other hand, cases that are highly idiotic have remained behind in growth only a little.
4. Further, there exists *a quantitative and qualitative difference in the disturbance in growth.* This in endemic cretinism is only delayed, also in the highest grades there occurs later closure of the most of the epiphysial junctures; the disturbance in growth is disproportionate (*Breus* and *Kolisko*).
5. *The hypophysis is often goitrously degenerated.*

I believe, therefore, that I shall have to concur in the opinion of those authors who ascribe to the noxus of cretinic degeneration a direct deleterious influence on the central nervous system and other tissues, probably also on the other ductless glands. Also this independent position that according to the later investigations we must ascribe to goiter heart is embraced in the confines of this view.

*On the other hand, the significant results of thyroid-gland therapy in many cases of endemic cretinism force us to ascribe to the athyrotic components a greater,* *indeed in many cases an almost determining significance.* The complete setting aside of this factor, as we see in the works of *H. Bircher* and *Scholz*, is not in my opinion correct. *E. Bircher* also surely goes too far when he explains the striking influencing of the inhibition of growth, which was observed in many cases of endemic cretinism under the thyroid medication, simply through the evidence that also the normal cartilages react to the administration of thyroid gland and that *Scholz* and *Zingerle* favorably influenced the growth of rachitic dwarfs through thyroidin tablets. Such results, that are to be striven after in all cases, are not to be attained in all. I quote examples of this in the chapter on infantilism, in which the inhibition of the osseous growth behaves refractory to thyroid therapy. The cause of the divergence of views I would especially see in the fact that *up to the present we have too little considered that a variable importance attaches to the athyrotic components in different individuals and in different epidemics.* So, for instance, in the epidemic that *Magnus-Levy* described it stood entirely in the foreground; it is not without significance in this respect that the epidemic that *Magnus-Levy* described had lasted only for a short time. Also in numerous cases of *Kocher* and *v. Wagner* is the athyrosis predominant. However, *v. Wagner* states that the cases originating in Judenburg did not react at all to the administration of thyroid. The same is true of the severest forms of cretinism in the Steiermark that *Scholz* observed, and of the cases of *Bircher.* It is therefore to be supposed that at different places the noxus works with different intensity. Further it would seem to be of significance whether the population has suffered from the affection for a long time; finally it is probable that bad living conditions, in-breeding, and many other factors contribute to the intensity and the clinical symptoms of the endemic.

How complicated the question is, is shown by a communication of *v. Wagner's* as to *marine cretinism.* It is known that the seacoasts are almost free from goiter and cretinism. Now *v. Wagner* observed on the island Veglia, belonging to the Guarneric Islands, fifteen dwarfs, mostly about 100 cm. tall. The closure of the fontanelles was delayed; in most, but not in all, was the root of the nose retracted, there existed more or less distinctly well-expressed myxedema of the skin, high voice; there was absence of hair on the pubic and in the axillary regions; the genitals showed high-grade infantilism, in men the mons Veneris was abundant in fat and, as is shown in the photographs accompanying *v. Wagner's* publication, was limited above by a horizontal line; frequently there existed constipation, dentition was delayed, the intelligence in some was only very slight, in others there existed only slight apathy; many could not read and write; the hearing was well developed in all. The thyroid gland was not palpable in all of them. *v. Wagner* discusses the question whether these cases are to be classified under endemic cretinism. As ground against such classification, *v. Wagner* adduces: the complete freedom from goiter of the neighborhood, the marked dwarfism of all individuals, the marked dysgenitalism, the normal development of hearing and the relatively good development of speech. *v. Wagner* believes that the in-breeding that exists on this island—also albinism is indigenous here—perhaps plays a rôle in this, but that also the insufficiency of the thyroid gland is the decisive factor. Very striking seems to me the circumstance that in all individuals at first the development was entirely normal up to the third, the fifth, indeed even the tenth year and the inhibition of growth did not set in until this age; the accompanying photograph shows, in addition to the marked dysgenitalism, a form of obesity such as we are wont to find in dystrophia adiposo-genitalis and to refer to the insufficiency of the interstitial glands or of the hypophysis. The disturbance of growth seems to me to speak decisively for the hypophysis. A strumous degeneration of the hypophysis could perhaps have been demonstrated by an enlargement of the sella on X-ray examination; in other cases there did exist, however, undoubted myxedematous alterations. Such an endemic degeneration of the ductless glandular system with predominant involvement of the glandular hypophysis occurring in earliest youth is, at all events up to the present, unique. I cannot at first hand answer with certainty the question as to whether or not a variety of cretinic degeneration exists in such a case.

Surveying once more the field covered in the preceding observations *it seems to me that the separation of the cretinic degeneration from the chapter of the pathology of the thyroid gland is indeed possible and desirable, on the other hand it would be a mistake to relegate too far to the background the intimate connecting associations with the thyroid gland.* The separate position depends on the localization to certain territories, depending on the fact that the noxus contained in the thyroid gland produces extremely frequently, perhaps even regularly, alterations not only in the thyroid gland but also in numerous organs such as the heart and the central nervous system.

But there are other attempts at explanation that I have not as yet mentioned. *v. Kutschera* supposes an infectious noxus; he bases the assumption on the following observation: dogs that have been brought up in the bed of a cretin remained behind in development and became typically cretinic. Of course it must be considered that these dogs were under the same external conditions as human beings and drank the same water. Very difficult to interpret is also the observation of *v. Wagner* that a dog with typical endemic cretinism shows extensive retrogression of the cretinic symptoms after extirpation of the goiter. *v. Wagner* assumes that the manifold symptoms of endemic cretinism are produced by a poison emanating from the goiter, and therefore, as previously mentioned, places the thyroid gland as the central figure in the pathogenesis.

**Differential Diagnosis.**—The differentiation between sporadic and endemic cretinism is often difficult and in certain cases may be impossible. The fact that the cretin comes from a locality in which cretinism is endemic naturally is not evidence, as sporadic cretinism may also occur in some infested neighborhood. The coming from a neighborhood where only goiter but not cretinism is endemic cannot without other factors be used against the diagnosis of endemic cretinism, as in such neighborhoods endemic cretinism may occur. I refer once more to the small endemic described by *Magnus-Levy*. Here too, seems to me, belongs the interesting observation of *Eller*. *Eller* describes three cases of cretinism in a Vienna family. The patients were goitrous and had never been out of Vienna; three sisters were entirely well; the cretins themselves had strumas. The result of the treatment with thyroid, which was not carried out perseveringly, was not satisfactory.

The finding of a struma, slight or absent myxedematous consistency of the skin, incongruity between mental development and the rest of the symptoms, relatively slight inhibition of ossification and closure of the fontanelles, unequal remaining behind of the epiphysial closures, slight or absent results of treatment, impossibility of stimulating the metabolism with thyroidin, low tolerance for thyroid-gland substance speak for endemic cretinism. As far as the disturbance in ossification is concerned, it must be considered that this occurs in many vegetative disturbances that have nothing to do either with the thyroid gland or with endemic cretinism. Already *v. Wyss* pointed this out; he found in four of seven individuals who, without showing striking symptoms of cretinism had remained behind physically and mentally, pronounced inhibition of growth and of ossification, which were in no wise different from those which are typical for endemic cretinism. We must therefore agree with *v. Wyss* that in a country in which cretinism is endemic the differentiation between cretins and idiots is extraordinarily difficult. The delay in ossification seems to be found regularly in cretinoids without mental defect.

### Addendum

Goiter is not at all uncommon in the United States. A close study would perhaps show that goiter is confined in this country to certain districts. *Clark* and *Pierce* mention that there are certain districts of endemic goiter in the region of the Great Lakes and certain sections of West Virginia. There is a well-known focus in Pennsylvania, in the vicinity of Wilkesbarre.

*McCarrison* was able to produce swelling of the thyroid experimentally in men by administering to them the filtrate of boiled water from a goitrous district. This author cites facts that make it very probable that the noxus of goiter exists in the soil, and may possibly be transmissible from individuals.

Blood counts from seventy-three cases of goiter made under the direction of *McCarrison* showed a lessening of the polymorphonuclear leucocytes in 98.9 per cent. of the cases and increase of the small mononuclear leucocytes in 92.5 per cent., an increase of the eosinophiles in 88 per cent., and an increase of the large mononuclear cells in only 23 per cent. of cases. The author regards as misleading and valueless *Kocher's* blood count as a criterion of differentiation between exophthalmic and nonexophthalmic goiter. He treats goiter, with striking reduction of the goiter, by the use of intestinal antiseptics such as salol and thymol, milk soured by the bacillus bulgaricus and the injection of vaccines prepared from bacillus coli. His publication contains a map showing how goiter is distributed.

*Gilbride* has made a bacteriological examination of the contents of eight cystic goiters, with negative results, save in one case in which he found the streptococcus vermiformis of *Sternberg*. *McCarrison* states that *Horand* has reported the presence of a parasite in a goitrous cyst, but added that in neither this work nor that of *Gilbride* is there sufficient evidence to justify the suspicion that the organisms found are causal agents in the production of goiter.

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# CHAPTER IV

## THE DISEASES OF THE PARATHYROID GLANDS

### (Glandulæ Parathyreoidæ)

### [Parathyroid Glandules, Epithelial Bodies, Epithelkörperchen]

**Anatomy.**—The parathyroid glands are organs arranged in pairs that show intimate spatial relationship with the thyroid gland. In man there are usually two parathyroid glands on each side. They have a length diameter of 3–15 mm. and a thickness or width of about 2 mm. According to *Erdheim*, the upper parathyroid glands (epithelial bodies) lie against the posterior surfaces of the lateral lobes of the thyroid gland about the middle of the height of the lobes, and the lower parathyroids lie toward the lower pole of these lobes, but not rarely there are exceptions with regard to both number and position of the parathyroids. On one side there may be as many as three or four of these bodies (*Schrieber et al.*); the lower bodies may lie as

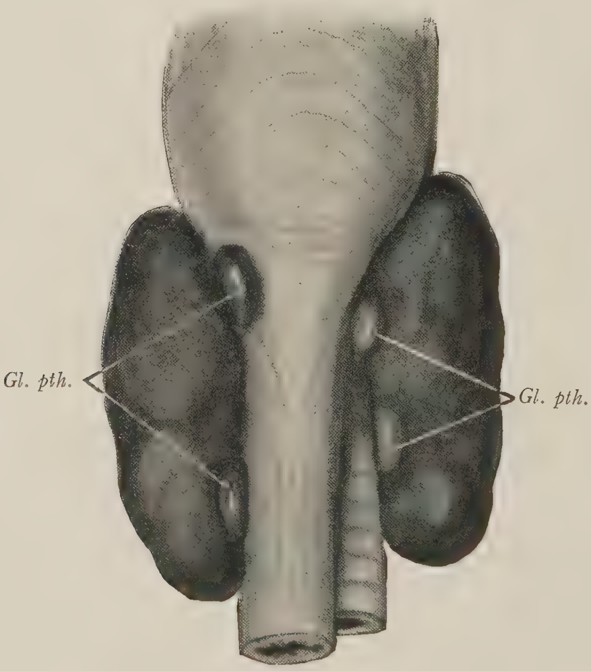

FIG. 23.—Parathyroid bodies of man (according to *Zuckerkandl*). Posterior view of organs of neck. *Gl. pth.* = parathyroid glands.

low as against the upper pole of the thymus. Statements exist even that accessory parathyroids are pushed down to the pericardial fatty tissue (*Vassale* and *Piana*). The bodies, especially the upper, are bound to the thyroid gland by connective tissue, and the upper may also in part be interpolated in the thyroid tissue. We find in the different species of animals great variations in the number and position of the parathyroids. In the cat, the upper parathyroid is always imbedded in the thyroid tissue; in the dog it is sometimes fully imbedded there (inner parathyroid, *Kohn*), so that extirpation of the parathyroids alone may be attended with great difficulty.

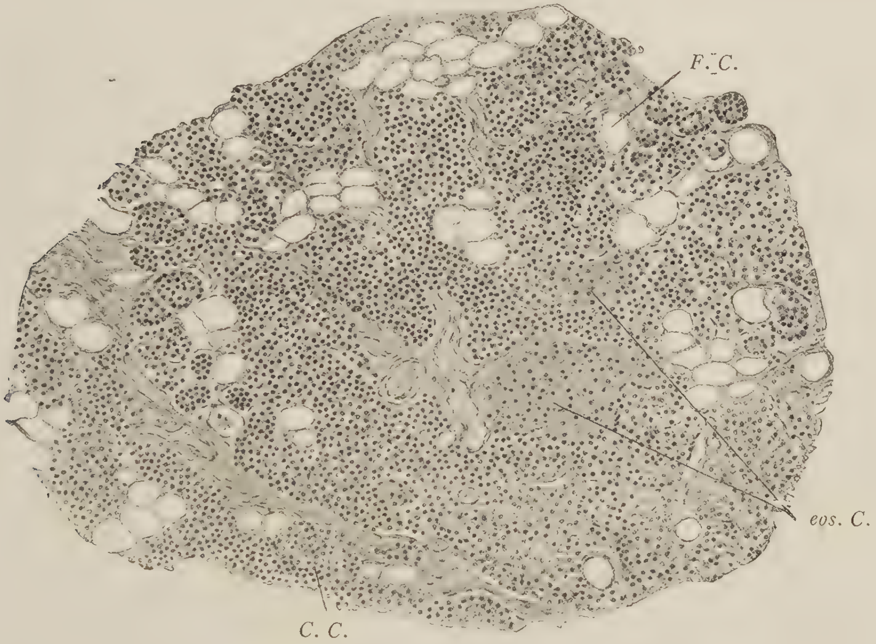

FIG. 24.—Parathyroid gland. *F. C.* = fat cells; *eos. C.* = eosinophilic cells; *C. C.* = chief cells.

It is especially important, moreover, that in herbivorous animals the parathyroids are entirely apart, spatially, from the thyroid gland.

The parathyroids are very abundantly supplied with blood. Between the individual cell groups are found numerous strikingly wide capillaries. The glands are supplied by the inferior thyroid artery.

Histologically the parathyroids are characterized by great richness in cells. According to *Welsh,* large polygonal chief cells and smaller so-called oxyphilic cells are to be distinguished from each other.

**Embryology.**—The parathyroids are entodermal glands (*Verdun*). Fig. 3 shows how the parathyroids and the thymus gland originate from the branchial arches.

The epithelial bodies ($e_3$ and $e_4$) come from the dorsal part of the third and fourth branchial pouch. The thymus gland comes from the ventral part of the third pouch.

If the bilaterally arranged thymus gland becomes pushed down the parathyroids may come to rest on the thymus gland or even to be included in its substance. From the illustration it will be also seen that the relationship of the parathyroids to the thyroid is purely topographical. $E_4$ represents the inner parathyroid gland which may eventually become included in the tissue of the thyroid.

**Historical.**—It will be seen from the intimate spatial relationship between the thyroid and the parathyroids why for a long time the functional independence of the parathyroids was not recognized. At the first attempts at total thyroidectomy, by *Schiff*, *Kocher*, *Rivardin*, *v. Eiselsberg* and *others*, there were observed, in addition to the results of the absence of the thyroid as described in Chapter II, severe acute manifestations that were uncommonly like the tetany that had formerly been observed in human pathology. The difference in topography of the parathyroids in different animal species, as just described, makes intelligible why in some species thyroid extirpation led to cachexia strumipriva, in others to tetany. The discovery, in 1880, by *Sandström*, of the parathyroids, first made a change in this respect. Indeed *Sandström* at first regarded the bodies described by him as the embryonal stages of thyroid tissue that had remained at a standstill; *Gley*, who in 1891 first discussed the physiological significance of the parathyroids, believed that these bodies would assume the function of the thyroid on extirpation of that gland. *A. Kohn* first taught the anatomical independence of the parathyroids; *Moussu*, and *Vassale* and *Generale* their functional independence. Also *Kohn* introduced the term "Epithelkörperchen." The investigations of *Pineles*, *Biedl*, *Erdheim* and others to-day place the independence of the parathyroids beyond question. The observations of aplasia of the thyroid with retention of the parathyroids, as detailed in chapter on the thyroid, showing the complete picture of deficiency of the thyroid with no symptoms whatever of tetany, further the fact that the absence or deficiency of thyroid gland only, not however that of the parathyroids, is made good by thyroidin therapy, and finally the fact established in animal experimentation that extirpation of the parathyroids alone leads to tetany but not to myxedema, *make certain the teaching of the physiological independence of the parathyroids and have furnished the demonstration that tetany has nothing to do with the absence of thyroid gland, but depends on an insufficiency of the function of the parathyroids.*

It is only one step from this knowledge to the view that the different forms of tetany observed in human pathology (parathyroprivic tetany), idiopathic or occupation tetany, tetany of children, tetany of maternity, stomach tetany, tetany in infectious diseases and poisonings, etc., depend on a uniform pathological basis, and that at the bottom of all is an absolute or relative insufficiency of the parathyroids (*Jeandelize, Pineles, Escherich, Erdheim, Chvostek, Jr., Rudinger*, and *others*).

### (a) Aparathyrosis or Hypoparathyrosis, Tetany

**Definition.**—*By tetany we mean an abnormally increased condition of excitement of the nervous system, that is demonstrable in a heightened excitability of the motor, sensible, sensory and vegetative nerves, and under certain circumstances, in paresthesias, and bilateral intermittent, for the most part painful, spasms, with intact consciousness, or becomes manifest through phenomena of irritation on the part of the vegetative nerves. To the picture of tetany belong also trophic and certain metabolic disturbances. The manifestations are the result of an insufficiency of the parathyroid glands.*

**Symptomatology.**—Increase in the *electric excitability* is to be regarded next to spasms as the most important cardinal symptom of tetany. It affects in the first place the peripheral motor nerves (*Erb*), although the sensory senses (*Hoffman*), and the nerves of special sense (*acusticus-Chvostek, Jr.*), are overexcitable to electricity. This hyperexcitability is found especially on the use of the galvanic current; the faradic excitability is most often normal. The ulnar nerve serves best for testing in adults; the peroneal nerve in children. We should use *Stintzing's* normal electrode (3 sq. cm.) and *Edelmann's* horizontal galvanometer. The hyperexcitability expresses itself not only in a lessening of the irritation threshold against the cathodal closing contraction, but also in a definite alteration of the contraction formula. In normal individuals the lower limits for the C.C.C. lies at about 0.9 milliampere for ulnar nerves, for the A.C.C. at about 1.5 to 2 milliamperes, for the A.O.C. about 2.5–3 milliamperes, for the C.C.Te about 5 milliamperes, and the C.O.C. can hardly be obtained even with high amperage. Now in tetany the C.C.C. can fall to very low values (as low as 0.1 milliampere, and also the values for A.C.C. fall (even to 0.5 milliampere); it is important, however, that the value for the A.O.C. fall and eventually become lower than that of A.C.C. and even lower than that of C.C.C. Further C.C.Te occurs at very low values, and finally also the C.O.C. may be obtained. Also A.C.Te and A.O.Te may be obtained sooner. The first statements as to the galvanic hyperexcitability came from *Kussmaul* and *Benedict;* first exact measurements were by *Erb.* In the tetany of children, first *Escherich* and *Jauregg v. Wagner* pointed out the galvanic hyperexcitability. *Thiemich* regarded the falling of C.O.C. below 5 milliamperes as conclusive for the diagnosis. It was shown, however, by *v. Pirquet* that this relation obtains only in the most severe cases and that the slight grades of tetany are first recognized in a falling of the value for A.O.C. in the so-called anodal hyperexcitability.

*Erb's* phenomenon may be present in the most of the motor nerves accessible for the test. For the most part it is present in like intensity in symmetrical nerves, although there are exceptions to this rule. For instance *v. Frankl-Hochwart* found in the right ulnar in a case a C.C.C. of 0.3 milliampere, in the left ulnar a C.C.C. of 0.1 milliampere. *Erb's* phenomenon, like all the symptoms of tetany, shows great variations. It is most distinct at the onset or during the acute exacerbations, less distinct, as a rule, during the intervals. In the chronic tetany that extends through many years the galvanic excitability can, during the interval free from attacks approach the lower limiting values of the normal, and may even show values as high as for normal individuals. As *v. Frankl-Hochwart* points out, this relation is beautifully shown in the tetany of maternity; here the galvanic hyperexcitability is shown only during pregnancy or lactation. *Erb's* phenomenon is the most important symptom of tetany, because we as yet know of no other condition in which it occurs. It is also very frequent. *v. Frankl-Hochwart* says that he has not seen any acute case of tetany with normal electrical excitability; exceptions do, however, extremely rarely, occur. *Kahn* and *I* observed a case of chronic tetany with acute exacerbations, in which all the important symptoms of tetany were present pronouncedly, but *Erb's* phenomenon, in spite of the presence of severe spasms, was absent during the first days. The condition ameliorated; *Erb's* phenomenon was positive only on an acute exacerbation of the illness, that occurred after about two weeks.

*A heightened excitability to the electric current is shown by the sensory nerves also* (*Hoffmann*). We usually test the ulnar nerve. Paresthesias occur in its distribution even on very low values of the C.C.C. There occurs too an analogous change in the sensation formula. Finally the *nerves of special sense may be hyperexcitable.* With relatively low current strengths, *Chvostek, Jr.*, found sensory reactions in the acoustic nerve with analogous alterations in the formula of sensation in six out of seven cases of tetany. *v. Frankl-Hochwart* found a similar relation to the galvanic current of the taste sensations. Occasionally, in testing the electrical excitability, when the electrode is placed over the mastoid process there occur with very low current strength, and often before the occurrence of contraction, ear noises and finally a bitter taste sensation (*Falta* and *Kahn*). Also these symptoms vary greatly.

Another certain symptom of latent as well as manifest tetany is the *mechanical hyperexcitability of the motor and sensory nerves*. *Chvostek, Sr.*, first pointed out in this regard, that in tetany percussion of the motor nerve trunks and especially the facial trunk leads to lightning-like contractions in the muscles supplied. When the facial trunk is struck, the contractions rarely affect the muscles of the forehead. *v. Frankl-Hochwart* distinguishes three degrees of the phenomenon depending on the intensity. In *Chvostek I* on percussion of the vicinity of the auditory meatus contractions occur in the muscles that close the eyelids, in those of the alæ nasi, and in those of the corner of the mouth. They may even be brought about by slight stroking of the front of the ear with the handle of the percussion hammer (*Schultze*). In *Chvostek II* there are contractions of the alæ nasi and muscles of the corner of the mouth on percussion under the zygomatic arch. In *Chvostek III* percussion here causes contractions of the corner of the mouth only. As to the pathognomonic significance of the different degrees of *Chvostek's* phenomena for tetany opinions are at variance.

The phenomenon is certainly very frequent in tetany, yet it may be wanting in pronounced cases and often shows great variations. On the other hand slight degrees of it may occur in numerous cases of neurasthenia, hysteria, and epilepsy. *v. Frankl-Hochwart* and *Schlesinger* found *Chvostek II* and *III* in nearly one-half of patients with phthisis. However, other authors, for example *Schönborn* (Heidelberg), do not find this phenomenon so frequent. It is found commonly also in rachitis. *Kahn* and *I* found it several times in rachitis tarda. *Mager* found it very frequently in enteroptosis, *v. Frankl-Hochwart* in strumous individuals. It is especially frequent in all possible sorts of cachexia, especially when this is associated with much loss of water from the body. *Curschmann* especially has pointed this out. *Kahn* and *I* observed it also in severe diabetes, and also in almost all cases of *Reichmann's* disease. It is probable that in a great number of such cases this phenomenon depends not so much on the mechanical excitability of the nerves as on that of the levator anguli oris muscle, as we tap too on the insertion of this muscle in the procedure. For this view speaks the fact that in the conditions named idiomuscular prominences were produced regularly on the various muscles.

*Chvostek II* and *III* are also seen not rarely in entirely normal individuals. Hence they are not pathognomonic for tetany, although it should be noted that these phenomena are very frequent in the localities in which tetany is endemic at the season of the tetany, and that in cases of tuberculosis in which they were present they were not infrequently found associated with caseation of certain of the parathyroids. *Chvostek I*, when pronounced, speaks very loudly for tetany; although absence of the symptom does not speak against tetany, as it may be wanting in the acute stages, and like all symptoms of tetany it shows great variations. The mechanical hyperexcitability of the sensory nerves expresses itself in the occurrence of a burning sensation on percussion of the nerve trunk or on pressure over the same. I shall speak later about the mechanical excitability of the sympathetic nerves of the blood-vessels.

*Trousseau's* phenomenon consists in the circumstance that pressure on a nerve trunk will bring about a typical tetanic spasm in the area of distribution of the same, or that the constriction of an extremity with a rubber bandage will also induce such a spasm. This phenomenon has nothing to do with alterations in the circulation, but depends on the excitability of the nerve itself (*v. Frankl-Hochwart*). However, it cannot be so simply explained by the increased motor irritability of the nerve alone, for *v. Frankl-Hochwart* saw bilateral spasms occur after pressure on the nerve plexus of one extremity, and *Schlesinger* shows that this phenomenon cannot be induced on the purely motor facial nerve, but only on the mixed nerve. Hence to the hyperexcitability of the motor nerves must be superadded that of the sensory nerves or of their spinal centers and their connecting links [Schaltstücke].

In similar manner would be explained the *leg-phenomenon* lately described by *Schlesinger*. On flexion at the hip-joint of the leg that is extended at the knee there can be induced under circumstances during the time of the freedom from attacks, a painful tonic spasm in the extremity, after from a few seconds to three minutes. Finally should be mentioned here the thermic hyperexcitability described by *Kashida*. This expresses itself in the occurrence of paresthesias and spasms on the application of cold or hot irritants.

In tetany the tendon reflexes are mostly normal, in the attack not rarely diminished.

Finally it should be mentioned that the patient frequently complains of *pains in the bones or joints* (*Falta* and *Kahn*), especially after severe tetanic attacks. I shall later report such a case.

We now come to a symptom that in the full development of tetany makes it one of the most dreadful diseases, and that has furnished its name, *i.e.*, the *tetanic spasm*. Here we meet with the greatest differences in the phenomena, and here the individual forms of tetany show the greatest variations in the localization of the spasm. In tetany of adults usually the upper extremities are involved symmetrically in the spasm, and indeed in the known obstetrician's position, yet there sometimes occur fist-positions with extended thumbs, and spasms may occur unilaterally (*v. Frankl-Hochwart, v. Jaksch, Curschmann, et al.*). When the lower extremities are affected, they are extended, the foot is in a slight equinovarus position, the toes are bent plantarly, sometimes, however, dorsally. The spasms are exquisitely painful.

As example I cite the following case (Case VI of *Falta* and *Kahn*):

*Observation XVII.*—Augustine Sch., four and one-half years old, from Vienna. Entered the clinic Nov. 24, 1911. For three weeks emaciation, and very poor appetite. One of the two children of the same parents died in 1909, in the first year of life, of spasm of the glottis. The patient herself had had spasms at two and one-half years, that lasted two days and were associated with fever. No rickets. Aug., 1910 to Jan., 1911 pertussis, then pneumonia with measles. Since that time frequent severe diarrheas for eight days; on Feb. 22 vomiting daily, since which six to seven bowel movements daily. Since this morning tonic spasms in the feet.

The illustration shows the typical obstetrician's position of the hands. Also there is distinct spasm of the left leg, as is to be seen by the tension of the tendon of the tibialis anticus muscle and by the dorsal flexion of the great toe. The diarrheas ceased on Feb. 15 (administration of tanningen), and the tetanic attacks disappeared.

In children there occurs the so-called carpopedal spasms in which the fingers do not, as in the previous case, assume the obstetrician's position, but are spread out. In involvement of the face, this expresses itself in a tension of the muscles, in spasm of the lids, in slight pointing of the mouth (fish-mouth position, "tetany face" of *Uffenheimer*), in spasms of the masseter, of the geniohyoglossus, and hyoglossus muscles (yawning spasms), in difficulty of speech on account of the tonic rigidity of the tongue, and eventually in convergence or strabismus with the occurrence of double vision. Sometimes the trunkal, nuchal, and abdominal musculature is involved. Finally the diaphragmatic and the intercostal muscles may be affected, producing dyspnea. *Bechterew* could produce spasm of the diaphragm directly by pressure over the phrenic nerve. As is known, the involvement of the muscles of the larynx is very common in children. Here the laryngospasm often stands well in the foreground. Moreover, the rest of the respiratory muscles are mostly involved. There occurs inspiratory retraction, and even lightning-like closure of the glottis (tetanus aponicus); more rarely expiratory apnea also (*Escherich*). Also in adults laryngospasms occur not at all rarely, as *Pineles* points out especially. Finally are yet to be mentioned the rare retching spasms. In the tetany of animals in which the parathyroids have been removed, these occur not at all rarely; here it is associated with vomiting. The transversely striated sphincters of the bladder and rectum for the most part remain free, although difficulty in urinating is sometimes seen (*v. Frankl-Hochwart*).

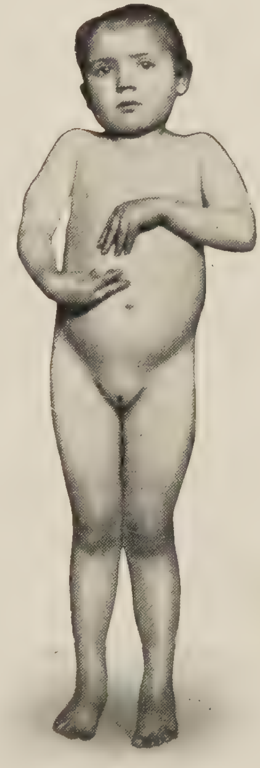

FIG. 25.—Obstetrician's position of the hands in tetany.

The duration of the spasms is often very short, although at times it lasts for hours. The patients often sit there for a long time with retracted abdomen, the extremities in the position described, incapable of movement. Sometimes there occurs only a single spasmodic attack; in other cases the attacks are repeated at longer or shorter intervals; in children are observed as many as eighty laryngospastic attacks a day.

The most manifold factors may bring about the spasm. In acute cases a slight excitation, percussion of the abdominal musculature, may lead to a spasm. In latent tetany a febrile affection (angina, tuberculin injection, gastrointestinal indisposition, introduction of the stomach sound, pregnancy, an intoxication, etc.) may render the tetany manifest.

*Chvostek, Jr.*, observed the occurrence of spasms after injection of tuberculin. *Rudinger* and *I* regularly saw spasms in the acute stages occur after injection of adrenalin. *Kahn* and *I* saw in the acute stage, also regularly, the occurrence of increase in intensity of the tetanic symptoms during the hours following the injection (as will be considered later).

Fibrillary contraction of the muscles, which are constant in the tetany of parathyroidectomized animals, occur in human tetany rarely. The same is also true as regard the pareses, which occur very frequently in totally parathyroidectomized animals, especially in the hind extremities.

Weakness of the extremities, especially after the spasms, may also occur in human beings. Also paralysis is observed in man (*v. Frankl-Hochwart*). *Chvostek, Jr.*, observed for instance a temporary paralysis in the ulnar territory after a spasm that was long in duration, which he attributed to the long drawn-out extreme position of flexion. Also slight ataxias occur in human beings as well as in animals. Spastic contractures are rare.

In adults, the sensorium is mostly uninvolved, in children it is very frequently clouded, although also in adults, in the severe cases, especially in the parathyroprivic tetany and in stomach tetany, there may occur clouding or indeed complete loss of consciousness.

The coincidence of *epileptic attacks* with tetany is not rare (*v. Frankl-Hochwart, Freund, Hirschl, Fries, Falta* and *Kahn, Redlich, et al.*). *Redlich* has collected seventy-two cases from the literature. Typical epilepsy may have existed for years, to which tetany is then superadded, or epileptic attacks may occur in the course of tetany, or may set in simultaneously with it. Especially in parathyroprivic individuals have been observed severe unilateral or bilateral epileptiform convulsions with loss of consciousness and slowness or absence of pupillary reaction. Such cases may rapidly come to a lethal end; or the tetany may altogether subside, and death follow later in status epilepticus, or tetany and epilepsy may pass over into a chronic stage (cases of *Westphal* and of *Redlich*). In children severe eclamptic attacks may enter into the course of tetany, or may occupy a position in the foreground. In the discussion of the pathogenesis I shall take up the question of the relation of the two conditions.

Finally it should be mentioned that in the severest forms of tetany, especially in the parathyroprivic forms and in stomach tetany, myotonic symptoms are observed not infrequently. *v. Frankl-Hochwart* designates them as intention spasms [Intentionskrämpfe]; they express themselves in such a manner that on such an attempted intentional movement as closure of the hand for instance, the hand cannot be opened again for several seconds

(*Schultze, Hoffmann, Bettmann, Kasparek, v. Voss, Schiefferdecker* and *Schultze, v. Orzechowski, et al.*).

In such cases we also observe mechanical hyperexcitability of the muscles and formation of pits on percussion, indeed even typical myotonic reaction on testing with the galvanic and faradic currents. We shall consider this more fully in the discussion of the pathogenesis.

I have already mentioned disturbances of the sensorium. In a series of cases psychoses have also been observed (*v. Frankl-Hochwart, Kraepelin, Hirschl,* and *others*). In acute cases, *v. Frankl-Hochwart* several times saw typical hallucinatory confusion or deep depression; he found abnormal psychical excitement and even depressive mental attitudes, fourteen times among thirty-seven cases. *Erdheim* saw characteristic conditions of excitement also in parathyroidectomized rats.

Finally it remains to be mentioned that in certain cases a slight grade of choked disc or neuroretinitis has been observed (*v. Jaksch, Hanke*).

I now come to the description of the behavior of the *vegetative nerves* in this condition. In the literature there have appeared up to the present only a few scattered references as to this question; nevertheless I can find ground for my statements in the work I did in collaboration with *Eppinger* and *Rudinger* and especially with *Fr. Kahn;* in addition, there is a detailed work on the subject by *Ibrahim.* The vegetative nerve show in tetany manifestations of increased excitability on one hand and long-continued heightening of tone on the other.

*Kahn* and *I* in one case observed hyperexcitability of the sympathetic nerves accompanying the vessels. After application of the bandage for the elicitation of *Trousseau's* phenomenon there occurred in addition to this phenomenon, pronounced anemia of the phalanges of the third, fourth, and fifth finger. Since that time I have seen this symptom once, in the case of E. C. to be described later (Observation XVIII). In this case there occurred regularly on application of the bandage to the upper arm or thigh, simultaneously with *Trousseau's* phenomenon, a pronounced anemia of the extremity. Here also belongs the pronounced dermographism that we find so extraordinarily frequent in the acute stage of the disease.

The electrical hyperexcitability of the vegetative nerves in man is hard to demonstrate. On the other hand, the chemical hyperexcitability as seen in the behavior of the patient on the action of adrenalin or pilocarpine may be shown. After subcutaneous injection of adrenalin in the acute stage of tetany there occurs almost regularly an abnormally strong action on the blood-pressure, on the heart action, on the contraction of the vessels of the skin, and also on the tetanic spasm. The increase in the blood-pressure and the pulse rate was especially rapid. To it was often added extreme paleness of the face and the skin of the entire body, strengthening of the heart action, subjective cardiac palpitations, and even extrasystoles. In almost all cases we saw an acute exacerbation of the tetanic conditions, and paresthesias or spasms. In the declining stage of the disease, all these manifestations were very much less pronounced.

An abnormally strong vascular action of the adrenalin could also be demonstrated on the parathyroidectomized dog.

Later in the consideration of the metabolism I will take up the question of the glycosuric action of adrenalin in tetany.

Also the sensitiveness to pilocarpine is essentially increased in the acute stage of tetany. There occurs abnormally strong outbreak of sweat or salivation, also flow of tears, initial contraction of the erectores pilorum muscles (gooseflesh), later marked reddening of the skin of the body with sensation of heat and rushes to the head, abnormal increase of the secretion of gastric juice and relaxations of stomach tonus; further, symptoms that we do hardly see on the administration of this pilocarpine; symptoms such as nausea, diarrhea, urinary and rectal pressure. Also pilocarpine induces frequent tetanic spasms in the various muscular territories. The manifestations of an increased tonus in the vegetative nerves in the first stage of tetany are of very manifold nature. Here I follow almost verbatim the expositions on the subject in the work of *Kahn* and *myself*.

Spasmodic conditions of the smooth ciliary muscle seem to occur very rarely. *Kunn* and *Fr. Müller* saw mydriasis in the attack (spasm of the dilatator papillæ?). *Feer* and also *Escherich* observed transitory differences in the size of the pupils, that *Feer* regarded as spasmodic conditions. *A. Fuchs* saw during the attack appreciable diminution in the time of pupillary reaction. *Finkelstein* saw pupillary rigidity. *Ibrahim* saw pupillary differences in one case (unilateral spasm of the dilator pupillæ). In this case the neck, pharyngeal and eye muscles were especially involved in the spasm, thus simulating the picture of a meningitis. The cerebrospinal fluid was clear however.

Little is known as to lachrymation in tetany; evidence as to the probability of its occurrence is furnished in one case only of *Kahn* and *myself*. Here there existed slight redness of the conjunctiva and there was often an increase in the lachrymation simultaneously with the exacerbation of the tetany, as well as an increased flow of saliva.

Also marked sweats are frequently found in the acute stage of tetany.

In tetany it is difficult to refer changes in the type of breathing to alterations in the tonus of the smooth musculature of the bronchi, as we must not overlook what part spasms of the diaphragm and of the intercostal muscles eventually play in its production. *Ibrahim*, *Finkelstein* and *Popper* report cases of tachypnea. We saw dyspnea occur very frequently.

Disturbances of the action of the heart seem to be very frequent. *Kahn* and *I* could observe in almost all cases in the acute stage strengthening of the cardiac action, loud sounds at the apex, and even accentuated second pulmonic sound, in one case an accentuated aortic second. To this is added lability of the heart action, in other words, slight tachycardia on psychical excitement and abnormally high pulse rate on working. Complaints as to cardiac palpitations are frequent. In two cases we observed, toward the end of the stay at the hospital, occurrences of mitral systolic murmurs that surely were not there previously.

Very noteworthy are the statements of *Ibrahim*. This author saw sudden death without spasm of the glottis in three cases of tetany of sucklings, without signs of suffocation showing at autopsy. Signs of status thymicolymphaticus were in these cases absent or only slightly developed. In two of these cases the heart was relaxed in dilatation. In the third case the right ventricle was relaxed, the left unusually hard and forcibly contracted. *Ibrahim* thought of tetany of the heart, probably called forth by vagal or sympathetic excitement. We do not as yet know how far abnormal conditions of excitability of the autonomous heart ganglia or heart regulating nerves are responsible for the manifestations mentioned.

In tetany of adults manifestations on the part of the *vascular apparatus* are very pronounced. In the acute stage all tetanics have pronounced vasomotor disturbances. They all look pale, in spite of the fact, that, as we shall see later, blood counts show high figures for red cells and a hemoglobin value not lowered. Emotions often call forth abnormally intensive variations of tonus in the vessels; and the edematous swellings that are observed not infrequently are to be regarded as angiospastic manifestations. *Ibrahim* saw, in a suckling suffering with tetany, edema of the legs, with kidneys intact, and *Kahn* and *I* several times saw marked edema of the skin over the metacarpo-phalangeal joints after severe attacks. *Curschmann* described pronounced angiospastic manifestations, vascular spasms of the fingers and toes. Heat relieved the attacks. Here too would belong the characteristic puffiness of the face which was first described by *v. Frankl-Hochwart* and which *we* have also frequently observed. The face is pale but does not possess the livid coloration that tends to appear in myxedema.

I now take up the question of the *blood picture* in tetany, as it stands in intimate relationship with the manifestations on the part of the vascular apparatus. Until the appearance of our work, the statements as to blood changes in tetany were concerned only with cases of so-called stomach tetany. In isolated cases there has been observed appreciable increase in the number of red cells, or increase in the specific gravity (*F. Müller*, *Fleiner*, *Kuckein*, also *ourselves*), and attempts had been made to refer these to the organism's poverty in water, that might have been brought about by deficiency in absorption on account of pyloric stenosis, or the vomiting of large amounts of gastric juice. Our investigations showed decisively that this polyglobulia is directly a tetany symptom. Above all, it could be shown that in the case of "stomach tetany" this polyglobulia existed only in the acute stages, and with the decline of the tetany it again made way for normal relations; the investigations also showed that the polyglobulia may be for a time appreciably increased during an acute attack, in one case rising from 5,106,000 to 7,808,000 red cells; finally, the investigations showed that in the cases of occupation tetany the red-cell count is higher during the acute stages, and that it is temporarily raised even higher during an acute attack. As example, I cite the following case:

*Observation XVIII.*—C. E. Entered the clinic May 14, 1912. Carpenter, forty years old. For about four years the patient felt a striking sensation of fatigue in the arms and legs, especially after heavy work and after long walks. He also had paresthesias in the arms and legs (formication, "going to sleep" of the left leg). For two years slight gastric disturbances, consisting in brief spasmodic pains, and in acid eructations, sometimes associated with vomiting. For the last year, the patient has felt quite well.

Two days ago he suddenly experienced nausea, acid eructations, vomiting and a colicky pain in the region of the stomach. Some hours later he experienced spasmodic drawing together of the hands (according to the description, the typical obstetrician's position), and formications in the tips of the fingers and twitchings of the muscles of the face. Later there were also spasms of the lower extremities, which became quite rigid. The spasms seem to have lasted three to four hours. The patient was conscious throughout the spasm. Since then the spasms have been repeated several times.

Rather strong potator. Inclination to bronchitides.

Rather vigorous, large patient, pale color of the face, facial expression as if he were going to cry, skin moist, apical dullness on the left, vesicular murmurs sharpened, at places rhonchial and whistling murmurs. Cardiac findings normal. Liver two fingerbreadths below the margin of the ribs. Very well pronounced dermographism.

*Chvostek I* and *II* strongly positive; also the frontal muscles twitch on application of the test; *Trousseau* markedly positive, *Hoffman* markedly positive, *Schlesinger* markedly positive.

| Electrical examination. | Ulnar | Facial |
|---|---|---|
| C.C.C. | 1.0 | 0.6 |
| An C.C. | 2.5 | 1.8 |
| An O.C. | 3.4 | 1.0 |
| C.C.Te. | 8.0 | 1.2 |
| An C.Te. | not attainable | not attainable |

Mechanical hyperexcitability of the muscles very pronounced. Idiomuscular ridges make their appearance.

Patellar reflexes markedly exaggerated, suggestion of a patellar clonus.

Coarse tremor of the fingers.

Blood-pressure (*Gärtner*), 125.

In urine traces of albumin, reactions for urobilin and urobilinogen markedly positive.

Tubercle bacilli in the sputum.

Increase of temperature up to 37.3°.

May 14.—During the day and also during the preceding night many severe tetanic spasms in the upper and lower extremities, that always lasted for several hours.

On elicitation of *Trousseau's* phenomenon by means of the bandage fibrillary contractions occur in the musculature of the arms or feet respectively. Together with the spasm there regularly appears, on application of the bandage, a pronounced anemia of the extremity in question.

May 15.—Severe attack this morning, at 10 o'clock, during which blood was withdrawn from the ear. The blood is dark red.

Erythrocytes, 6500,000.
Leucocytes, 4200, of which:
Polymorphonuclear neutrophiles, 63 per cent.
Large mononuclear cells, 36 per cent.
Eosinophiles, 1 per cent.

May 16.—Blood findings during the attack-free interval.

Erythrocytes, 5,600,000.

*Trosseau* positive; after the decline, the patient complained of severe bone pains in the extremity affected.

May 20.—No attack since the 16th. Face still slightly swollen, facial expression still somewhat as if the patient were going to weep.

May 22.—Eyrthrocytes, 5,200,000.

May 24.—*Trosseau* can no longer be elicited.

May 25–31.—Patient feels well, no paresthesias; he has gained as much as 5 kg., appetite excellent, no gastric disturbances.

In a case reported by *Falta* and *Kahn* the following values were found: At the beginning of the observation about 4,000,000 erythrocytes and 9 gm. hemoglobin. Three weeks later during a long-continued severe attack 7,808,000 erythrocytes and 14.86 per cent. hemoglobin. The next day, during a period of almost free attacks there were 5,106,000 erythrocytes. Later after amelioration of the spasms 4,160,000. This was a case of tetany in the course of a *Reichmann's* disease. In another case (Observation XXIII) that I report below, we likewise see a distinct agreement between the variation of the erythrocyte count and the tetanic condition. I would suppose that the behavior of the erythrocytes furnishes a good criterion for the course of the disease, just as the leucocyte formula does in Basedow's disease.

In dogs, also, we have seen, after parathyroidectomy, the count of erythrocytes in the acute stage rise to 7,000,000. Such polyglobulias occurring during the acute stage can be explained in no other way than that they are due to vascular spasm, analogous to those polyglobulias which are observed after injection of adrenalin (*Bertelli*, *Falta*, and *Schweeger*). But we are not justified in assuming, on this account, that during the tetanic attack there is an increased production of adrenalin; we should rather suppose that in analogy with all other conditions of excitement in tetany the seat of the hyperexcitability is to be found in the ganglia. We have noticed no increase of blood-pressure during the attack, which however does not speak against our supposition—for vascular spasm need not occur in all portions of the body simultaneously and thus an equalization may occur very readily. The polyglobulia of the so-called stomach tetany is to be explained in the same way.

The *leucocyte* count in tetany is mostly normal. Leastwise in individual cases, we saw, during severe attacks, transitory hyperleucocytosis up to

19,000. Differential counts of the leucocytes showed, in the great majority of cases, a rather distinct lymphocytosis or a relative and absolute diminution of the neutrophilic cells. In these cases there also were found, for the most part, swellings of the lymph glands at the portions of the body accessible to palpation, enlargement of the tonsils and papillæ of the base of the tongue, hence a slight status lymphaticus.

With more exact investigation, there could also be demonstrated in the great number of cases of tetany slight or severe disturbances in the function of the *gastrointestinal tract*. In this connection we could distinguish two categories of cases. In one the tetany develops in individuals who have been sick for a long time with gastric and intestinal complaints, especially with those which lead to a high-grade stagnation of the gastric or intestinal contents. To this group I shall refer more in detail in the consideration of the individual forms of tetany. In the second category the gastrointestinal disturbances occur at or after the outbreak of the tetany. Many such cases have been observed by *Kahn* and *myself*. Of such disturbances I would mention: First, a certain hyperexcitability which, as already mentioned, manifests itself in the experiment with pilocarpine in an abnormally marked laxity of the stomach and in a very pronounced stratification of the gastric contents, eventually in tenesmus and diarrheas. Second, manifestations of increased secretion of the gastric or intestinal glands; in certain cases there is found for example a slight grade of hyperchlorhydria, such has been described by *Jonas* and *Rudinger*. On increased secretional processes in the intestinal tract may depend the diarrheas we observed so frequently. In many cases the tetany is ushered in with diarrheas or vomiting.

As example I cite the following:

*Observation XIX.*—A. W. (Case VII of *Falta* and *Kahn*), twenty-seven-year-old woman from Vienna. Entered the first medical clinic March 16, 1909. Marked chlorosis at the age of sixteen. Periods from the age of eighteen on, regular. Three normal confinements. Three days ago suffered with severe pains in the abdomen, that were associated with fever, eructations, and constipation. On the next morning typical tetanic spasms in the upper extremities, hands in the obstetrician's position, flexion at the elbows, upper arms drawn to the body. At least six such attacks each of about five minutes, duration. The spasms were painful. The galvanic excitability was increased. Rapid recovery.

Still more instructive is the following case, in which the gastric disturbance set in at the same time as the tetanic spasms:

*Observation XX.*—L. E. (Case VIII of *Falta* and *Kahn*), twenty-year-old woman from Vienna. Entered the first medical clinic on March 23, 1911. One normal confinement. Present illness began six days ago with severe pains in the back and hypogastrium, with the vomiting of green-colored masses of bitter taste, and a painful spasmodic attack affecting the hands and legs. The hands were in typical obstetrician's position. Two days later again severe pains in the abdomen, with vomiting, associated with typical attack of tetanic spasms in the upper extremities and later abdominal pains of a twitching character. Temperature as high as 38°. Indican much increased. Rapid recovery.

In other cases the gastric disturbances occur later, and are made worse by a later exacerbation of the tetany. We find likewise that in the cases of the first category the gastrointestinal disturbances may increase markedly at the time that the tetany is added to the clinical picture.

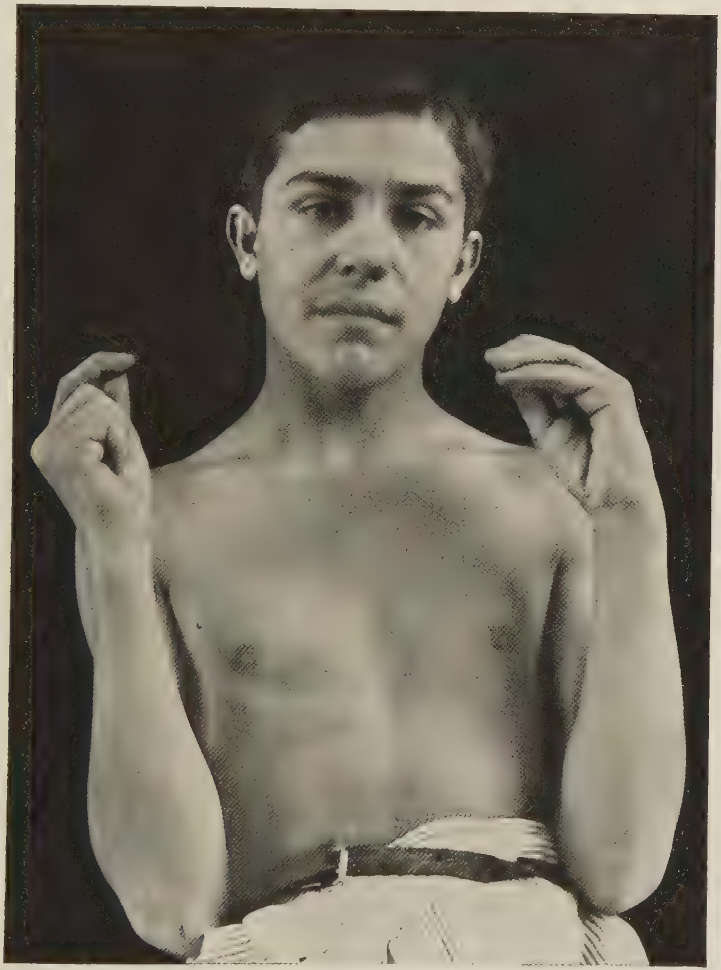

FIG. 26.—Tetany face (Observation XXI).

In many cases, as seen by X-ray screen, there is an abnormally rapid emptying of the stomach. In some cases there is a marked pyloric spasm, in the acute stage, that leads to acute dilatation of the stomach. The cases that belong here, which *Kahn* and *myself* have reported, are those of the first category, in which gastric disturbances have existed previously. It is probable that the tetany increases the pyloric spasm, or in many cases directly brings it about. A short time ago, I saw also a case of typical occupation tetany that showed the same thing. The report of it follows:

*Observation XXI.*—B., seventeen years old, shoemaker. Entered the clinic Jan. 14, 1913. First attack of tetany in winter of 1911. The convulsions then lasted with interruptions throughout the winter, disappearing only in April. Throughout the summer, the patient felt quite well; two days ago spasms reappeared, especially in the upper extremities, and to it were added formications. The symptoms, varying in intensity, have lasted until to-day.

The patient shows the typical crying facial expression of the tetanic. There exists great vasomotor excitability. All the typical symptoms of tetany are present. The galvanic excitability is much increased. The examination of the blood shows 6,250,000 erythrocytes. There exist painful spasms, especially in the upper extremities, that are often repeated throughout the day. Temperature as high as 37.5.°

Jan. 18.—For three days no spasmodic attacks, the electrical excitability is less increased; in blood, 4,870,000 erythrocytes. *Chvostek's* and *Trousseau's* phenomena no more elicitable.

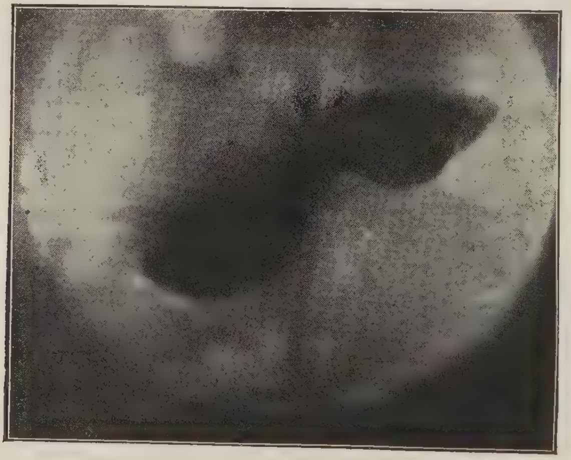

FIG. 27.—Spasm of the stomach in tetany (*Falta* and *Kahn*, Ztsch. f. klin. Med., Bd. LXXIV).

Jan. 23.—Fresh spasms, the symptoms of tetany present once more, 5,820,000 erythrocytes.

Jan. 24.—X-ray examination two hours after breakfast shows a *dilated stomach filled to a marked degree with fluid, which reaches to three finger-breadths below the umbilicus; there exists lengthened time for emptying of the stomach, in short, signs of a hypersecretion with pyloric stenosis.*

Jan. 31.—*Chvostek* still positive, spasms anew, 6,400,000 erythrocytes.

Feb. 6.—No spasms any more, but there still exists paresthesias. *Chvostek* and *Trousseau* negative.

From now on the tetanic symptoms decline, the count of erythrocytes becomes normal (4,500,000–4,800,000), the X-ray examination of the stomach, that has been taken three times in the course of the last two weeks, now always shows normal relations; after a breakfast the X-rays show that the stomach reaches to two finger breadths below the umbilicus. Peristalsis and time of emptying are now normal.

In this case, therefore, is to be found an "attack" of pylorospasm and hypersecretion and consecutive dilatation of the stomach occurring in the

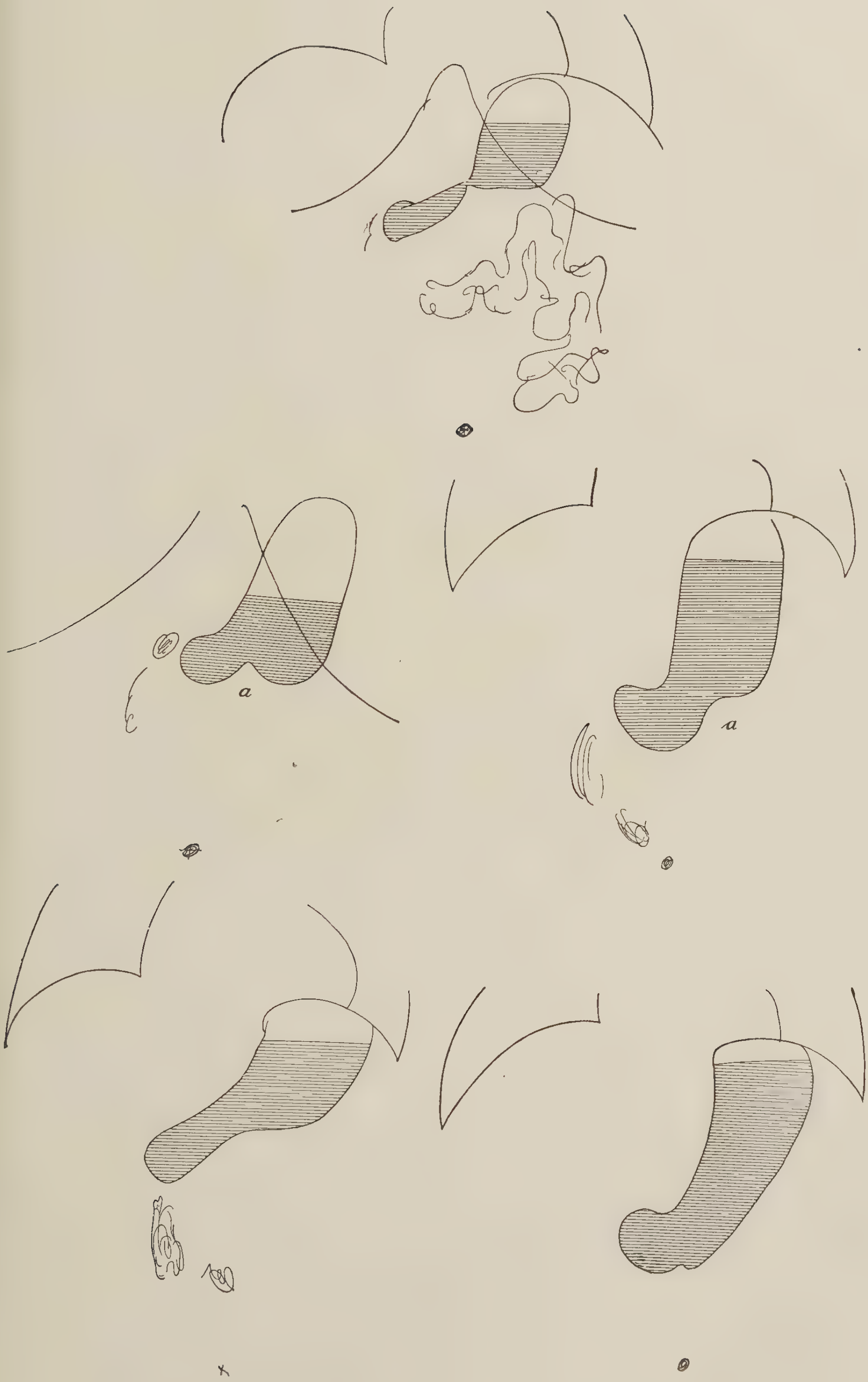

FIG. 28.—Spasm of the stomach in tetany (after *Falta* and *Kahn*, Ztsch. f. klin. Med., Bd. LXXIV).

acute stage of tetany. Also *Ibrahim* is of the opinion that the pylorospasm can occur in the course of a tetany of childhood.

Especially significant for the question we are here dealing with are two observations that have been reported by *Kahn* and *myself*. I would therefore go into the question more accurately at this point. In the one case (Observation XXII—Case 18 of *Falta* and *Kahn*), X-ray examination at the time that only slight signs of tetany existed showed an elongated but otherwise normal stomach. On a later examination, during an acute exacerbation of the tetany, there was found a retraction of the greater curvature, completely the picture of an hour-glass stomach (see Fig. 27). The tetanic spasms rapidly decreased in intensity, the stomach assuming normal relations after a few days. In the case there were no grounds for the assumption of an ulcus ventriculi. In a second case (Observation XXIII—Case 17 of *Falta* and *Kahn*) the stomach, as found on X-ray examination at the time of an acute exacerbation of the tetany and indeed during an attack, was small, markedly contracted, divided in two parts like an hour-glass stomach; in addition there was insufficiency of the pylorus; there was present therefore a total spasm of the stomach, that affected also the longitudinal musculature. At the next examination, this phenomenon occurred again, gradually decreasing in intensity, however, with the amelioration of the tetany; and later, when the tetany had disappeared entirely, the stomach showed normal relations on X-ray examination (see Fig. 28). We regarded these manifestations as conditions of tetanic spasms.

Also in thyroprivic animals I several times observed that the spasm was ushered in with vomiting and bowel movement.

All observations detailed point to the fact that in the acute stage of tetany the gastrointestinal tract may show symptoms of increased excitability and a heightened tonus, which later may increase up to a spasmodic condition. To which are added heightening of the secretory processes.

*Ibrahim* further describes, in the case of suckling tetany, spasm of the sphincter of the bladder that led to marked retention of urine, and mentions similar observations of *Sachs*, *Escherich* and *Hagenbach-Burckhardt*. *v. Frankl-Hochwart* had mentioned still earlier a retention of urine in tetany of adults. *Ibrahim* further assumes involvement of the sphincter ani in the tetanic spasms as he often observed in suckling tetany an intense gaseous distention of the abdomen (flatulent colic). After introduction of an intestinal tube there were emptied large amounts of gas—or even spontaneously there occurred an "explosion-like expulsion of flatus with frequent clonic twitchings of the abdominal muscles." Also *Koeppe* had already supposed, as *Ibrahim* states, that the internal sphincter became contracted in the eclamptic attack.

Finally we mention the disturbances of the *regulation of heat*. In parathyroprivic dogs there often occur, during attacks, increases in temperature;

in very intense spasms we even observed on several occasions values signifying hyperpyrexia. Such disturbances of heat regulation also occur in human tetany. In the attack-free interval, the body temperature, as *v. Jaksch* and *v. Frankl-Hochwart* have emphasized, is often abnormally low. In thirty-five observations on acute cases *v. Jaksch* saw more or less fever at the beginning of the disease nine times. *Kahn* and *my* observations agree with these. We frequently saw with the acute stage temperature as high as 37.8°, in one case up to 38.5°, without that exact investigation afforded any ground that there was any cause for the increase of temperature other than the tetany. Later, after decline of the tetany, the temperature sank to normal or slightly subnormal values. In certain cases we found in the acute stage transitory rises of temperature after the injection of substances that otherwise do not tend to induce fever (antithyroidin (*Möbius*), pituitrium glandulare of *Parke, Davis & Co.*). This points to an especial lability of the regulation of heat. One could be tempted to regard the increase of temperature in the sense of those authors who consider idiopathic tetany as an infectious disease. The fact that it is found to still higher degrees in experimental thyroprivic tetany has led *Kahn* and *myself* to the assumption that it is probably the expression of a condition of excitability of the vegetative nerves.

Summarizing again all observations that can be advanced for the vegetative organs, we find *that in the acute stage of tetany* the hyperexcitability or the abnormal conditions of irritability are *not limited throughout to the central nervous system and to the peripheral nerves but they involve also the vegetative nervous system.* With the decline of the acute tetanic condition there also occurs a decline of the condition of irritability of the vegetative nerves.

Also the *metabolism* in tetany shows alterations.

Disturbances in the *carbohydrate metabolism* are almost constant in the tetanic dogs. First a few remarks as to the glycosuric action of adrenalin in tetany. In the thyroidless dog it is known that the glycosuric action of adrenalin is reduced. In dogs that have had only their parathyroids removed it is mostly increased, so far as a tetanic spasm is not induced by the injection (*Eppinger*, *Falta*, and *Rudinger*). In the idiopathic human tetany *Rudinger* and *I* never found in the acute stage glycosuria following injection of adrenalin; but on the contrary, as already mentioned, almost always a strong reaction of the cardiovascular apparatus. This dissociation of the action of adrenalin has its foundation chiefly in the increase of sugar consumption through the enormous vasoconstriction and eventually in the attack induced by means of injection. In the declining stage of tetany we find, contrariwise, frequently a distinct glycosuric action due to adrenalin.

In parathyroidectomized dogs the assimilation limits for dextrose are regularly reduced. *Falkenburg* and *R. Hirsch*, and also *Frank P. Underhill* and *Tadasu Saiki*, found this after thyroparathyroidectomy and referred it to the absence of the thyroid gland. This, however, leads to a heightening of the tolerance boundary. According to the experiments of *Eppinger, Rudinger*, and *myself* the glycosuria after thyroparathyroidectomy depends on the absence of the parathyroids. In a dog almost completely parathyroidectomized we found that when a diet rich in starch was administered even large amounts of sugar would appear in the urine for a long time. After the extirpation of the pancreas and three parathyroids we found in many experiments a higher D to N quotient than could be obtained on extirpation of the pancreas alone. In human beings ill with tetany we never found reduction of the assimilation limits for dextrose, and *Kahn* and *I* can adduce an observation that shows that also in human beings the insufficiency of the function of the parathyroids exercises an indirect influence on the function of the pancreas. In a case of Basedow's disease complicated with tetany the test for alimentary glycosuria immediately after the tetanic attack yielded 4.1 gm. of sugar. Later after the acute tetany had subsided many tests for alimentary glycosuria resulted negative. In the literature is found only a statement of *Miller* that he observed transitory glycosuria after an attack of tetany.

*MacCallum* and *Vögtlin*, and also *we*, saw the *albumin exchange* in parathyroidectomized dogs appreciably increased. There do not exist similar investigations on human beings. There also occur regularly disturbances of the intermediate albumin exchange. *MacCallum* and *Vögtlin* found in thyroparathyroprivic dogs increase of the elimination of ammonia in the urine and of the quotient $\frac{NH_3N}{N}$, and in addition increased creatinin elimination. In human idiopathic tetany *Kahn* and *I* found in the acute stage the elimination of ammonia for the most part relatively and absolutely increased. The amino-acid fraction was for the most part normal; on the contrary, the peptid-N in our experiments was often even appreciably increased. Administration of glycocoll increased this value mostly only unessentially. Immediately after the decline of the acute tetany this value for the peptid-N was mostly still high, but distinctly lower than in the acute stage, or it had already become normal. Also the heightening of the ammonia value can apparently outlast for some time the acute stage. The findings described are to be distinguished from those in lesions of the liver in that in the latter the amino-acid-N is ordinarily increased as much as or even more than the peptid-N, and the administration of glycocoll almost always causes an increase of these factors. Perhaps these disturbances of the intermediary metabolism in tetany are the expression of a condition of nervous hyperirritability of the liver.

Systematic investigations as to the *gaseous metabolism* in tetany have as yet not been made. That the exchange of calories in the acute stage and especially in the severe attack is markedly increased needs no especial investigation. More interesting would be the investigation of the fundamental exchange in chronic tetany. Partially parathyroidectomized animals often show a severe cachexia; and often in human idiopathic tetany, cachectic manifestations later make their appearance (*v. Frankl-Hochwart*). The cases of relapsing tetany that *Kahn* and *I* observed all showed more or less distinct signs of cachexia (see later the relations to the thyroid gland). Here there must be a profound disturbance of metabolism, as has been mentioned by *Segale* and *others*.

The behavior of the *calcium metabolism* in tetany has been much studied. Stimulating were the observations of *Sabbatani* and *Loeb*. *Sabbatani* found that application of calcium salts to the surface of the brain reduced the excitability, application of sodium salts increased it; *Loeb* found that substances that precipitate calcium heightened the excitability of the nerves. This holds true also for the vegetative nerves (*R. Chiari* and *A. Fröhlich*). *MacCallum* and *Vögtlin* as well as *Parhon* and *Orechie* have tried to influence favorably the tetanic spasms of parathyroidectomized dogs by the subcutaneous or peroral administration of calcium. Magnesium salts work directly as do the calcium salts, but show in addition strong toxic action. Potassium salts increase the irritability. *Quest* had already stated before this that the brain of new-born infants, which is relatively slightly excitable, is very rich in calcium, but that later the calcium-contents of the brain reduces. He further states that diet poor in calcium makes the animal hyperexcitable, and that the brains of children after they have died of tetany are very poor in calcium. *MacCallum* and *Vögtlin* found the calcium-contents of the brain of parathyroidectomized dogs lowered, also those of the blood. The elimination of calcium through the urine and feces was increased. This last fact was also found by us. The same was also observed by *Cattaneo*. *Neurath*, who estimated the so-called active calcium in the blood of children with tetany by *Wright's* method, found very low values. Investigations as to the calcium balance in children with tetany frequently show increased elimination of calcium (*L. V. Iddo* and *Sarle*, and *others*). *Aschenheim* has recently pointed out that there does not exist so much an absolute calcium poverty of the tissues as there does [an increase of] the relation of alkalies to earthy alkalies. He found in children who had died of spasmophilia an increase of this quotient just as in parathyroidectomized dogs. *Finkelstein* and *Rosenstern* arrived at similar views. According to *Rosenstern* the administration of common salt to children brings forth anodal hyperexcitability, and indeed even laryngospasm.

Experimental investigations show also that the function of the parathyroids influences bone formation. *Morel* and *Canal* found in parathyroidectomized dogs that the healing of fractures is delayed and the callus formation slowed. *Erdheim* showed that such callus is remarkably poor in calcium. *Leopold* and *v. Reuss* found the skeletons of youthful parathyroidectomized rats poorer in calcium than those of the control animals. To a loss of calcium the parathyroid insufficiency points also to the finding of *Schüller* that the bones in chronic tetany show in the Röntgen picture a characteristic rarefaction of the trabeculæ and marked atrophy, an observation that we could confirm in almost all the cases, in which we paid attention to it. We found this, however, in cases that had never had tetany.

Summarizing that which has been said as to the metabolism, we find that *in the acute stage of tetany there exists an appreciable increase of the metabolism, that is related to very many factors of the same.* As most probable, we may suppose that only in experimental, but also in human, tetany there exists an *increased breaking down of albumin with disturbances in the intermediary albuminous decomposition, increased exchange of carbohydrates, increased production of calories, and apparently also increased elimination of calcium.* A part of these alterations in metabolism may well depend on increased irritability in the vegetative nervous system. We may expect in the chronic stages of tetany alterations of metabolism that to-day we cannot well define.

The **trophic disturbances** in tetany affect epithelial parts exclusively, the hairs, nails, skin, enamel, and ciliary epithelium. In chronic tetany there are frequent statements as to a thinned-out growth of hair (*Hoffmann, v. Frankl-Hochwart*, and *others*). An acute exacerbation may be introduced with *rapid falling out of the hair. Adler* and *Thaler* in their experiments on dogs found the falling out of hair directly a premonitory symptom of tetany.

Also *Pfeiffer* and *Meier* observed in ectomized animals falling out of hair as the direct symptom of tetany. *Speigler* in a case of chronic tetany found that the thinned-out and very thin hair was split at the point (*trichorrhexis*). Also the nails frequently show trophic disturbances, they become *brittle* and there may occur *complete necrosis* that leads to casting off of the nails; rapid substitution occurs, however, after subsidence of the acute stage. In a new attack the process may be repeated. An instructive case is reported by *Hoffmann.* It is that of a woman who had passed through five normal deliveries. After the fifth pregnancy, she developed tetany with distinct edema of the hands. The finger nails fell out. A year later tetany recurred. This time the hair fell out. After a year, new pregnancy and tetany; after the delivery again trophic alterations of the finger nails. After a half year, at the time of a new pregnancy, again tetany, with which was associated loss of nails and hair. In the tetany of children loss of the finger-nails seems to be very rare. *Pineles* found in the literature only one observation by *Hoffmann,* in a three and one-half-year-old child.

The *skin* of the face and of the extremities shows in acute cases a *puffy appearance* (angiospasm [?], see what is stated previously). On account of this the face takes on a characteristic expression of crying.

*Pigmentations* of the skin are rare. *Kocher* states that after total excision of the thyroid gland in many individuals there occur, if the tetany symptoms predominate, marked pigmentations progressing as far as bronzed skin

Of greatest interest is the *formation of cataracts.* Already *Meinert* had observed in tetany a case of cataract, and the first exact investigations began with *Peters.* Important information was furnished by *Ernheim, Pineles, Zirm, Sperber, Bartels, v. Frankl-Hochwart, Schönborn* and *others.* The cataract of tetany is characterized by its very rapid development. It is not at all rare in children. It is especially frequent in the tetany of pregnancy, and in women between the ages of eighteen and forty years, as observed by *Zirm* and *Sperber.* In youthful individuals it occurs more frequently as nuclear cataract, in older individuals as cortical cataract. *Peters* was the first to show that the cataract formation was brought about by degenerative changes in the ciliary epithelium. This caused a molecular concentration of the water in the chamber, thereby damaging the lens. *Erdheim* produced tetany cataract by parathyroidectomy in rats. We are indebted to *Pineles* for the information that the cataract formation occurs in all forms of tetany.

*Hanke* on histological examination of the globe of the forty-nine-year-old man who suffered with chronic tetany and cataract found optic neuritis and a characteristic degeneration of the pigment epithelium of the posterior surface of the iris, similar to that observed in diabetes mellitus. *Pineles* had already attached theoretic value to the circumstance that cataract formation could occur in tetany as well as in diabetes.

Of recent date are the investigations concerning the disturbances in *tooth formation.* *Erdheim* first observed that there occurred in rats, one and one-half to two and one-half months after the operation, opaque spots on the anterior surface of the incisor teeth which gradually advanced toward the points with the teeth's growth. Either the tooth breaks off at this point or the defect in the enamel heals, leaving behind a shallow groove. The tooth may also break in the alveolus, in which case suppuration of the latter occurs. *Erdheim* observed a deficient calcification of the dentine. Even the short cessation of parathyroid function that occurs in autotransplantation of the parathyroid is sufficient to determine the appearance of stripes poor in calcium in the dentine of young rats. An especial clinical interest to *Erdheim's* studies is given by the investigations of *Fleischmann.* This worker held the view that the defect of enamel so commonly observed was due, not as was formerly supposed to rachitis, but to tetany. He points to the disproportion between the frequency of rachitis and hypoplasia of the enamel. In rachitis are regularly found alterations in the dentine; in tetany, however, always hypoplasia of the enamel leading to the formation of horizontally coursing transverse surfaces. When frequent exacerbations of the tetany have occurred, are found numerous furrows below one another. *Fleischmann* investigated ten children who had suffered from tetany and found in all the above-mentioned hypoplasia, and indeed this was present only on those teeth that had been present during the course of the illness. Nearly all of the children had also had rachitis. *Fleischmann* points out, however, that rachitis lasts much longer than tetany, and also attains its acme much later. *Fleischmann* also finds support for his view in the statement of *Fuchs* that children with lamellar cataract almost always show hypoplasia of the enamel. In individuals with hypoplasia of the enamel, in whom nothing is known of their having had tetany, there may have existed a latent tetanic condition in early childhood. Very convincing is an observation of *Spiegler* in a case of recurring tetany, in whom there was an attack every spring during eight years. In this case it was known that the tetany had at first made its appearance at the end of the second year of life. All teeth whose crowns must have been formed at this time were normal, while the teeth whose crowns developed later showed defects of the enamel. An entirely similar case was observed by *Kahn* and *myself* (Observation XXIII). Here were found on the canine and incisor teeth punctiform defects of enamel often standing in parallel rows; the upper parts of the molars were partly broken off. The patient's mother stated definitely that already in the first year of life, but more especially in the second and third years, he had spasms of the glottis and spasms of the hands, while a severe rachitis was added to the picture only in the third year.

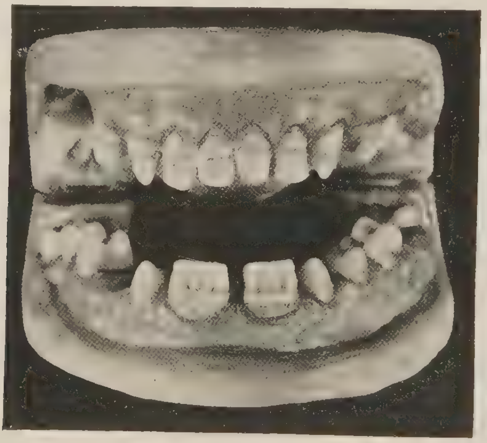

FIG. 29.—Enamel defect in tetany.

The above illustration (Fig. 29) shows the defects of enamel observed by us in another case.

The connection between tetany and defects of the enamel is by all this evidence put on a sound basis; and I shall put aside the discussion of the possibility of these defects being brought about by other causes.

Perhaps the *conjunctivitis* accompanying tetany may also be regarded as a trophic disturbance. *De Quervain* observed that parathyroidectomized dogs often suffer from severe conjunctivitis. I saw this almost regularly in parathyroidectomized dogs and cats. In the case previously mentioned (Observation XXIII) it happened that the conjunctivitis regularly became exacerbated with the aggravation of the tetany.

Yet a few words with regard to *growth disturbances* in tetany. *Schüller* investigated five cases of rachitis tarda and found besides pronounced *Chvostek's* symptoms, remaining behind in growth, delayed ossification and dentition, and marked atrophy of the bones; the last was also found in an exactly investigated case of the chronic recurring form of tetany, and also in three juvenile cases of occupation tetany. On the contrary, a case of tetany after strumectomy and some cases of tetany of maternity showed normal relations. *Schüller* points out that tetany may also occur in combination with osteomalacia, and believes that tetany may induce rachitic alterations before the cessation of bone growth, and osteomalacia after it. A similar view is held by *Erdheim* on the basis of histological examination of the skeleton, and especially of callus formation in rats after parathyroidectomy. *Kassowitz* had before this supposed a casual connection between rachitis and tetany.

This view I would not subscribe to. It is to be expected that high-grade, and especially, long-continued absence of parathyroid function in youthful life would lead to disturbances in growth of bones. We also saw certain cases of chronic recurring tetany, in which the individuals were remarkably small and showed retarded epiphysial closure. The disturbance has certainly nothing to do with true rachitis. Sometimes, indeed, it is difficult to separate the two conditions, as combinations of rachitis and tetany are extremely frequent, and according to *Escherich*, not less than 80–90 per cent. of all tetany in children is associated with rachitis, although there are certainly cases of tetany without rachitis, and above all, cases of rachitis with tetany constitute only an extremely small percentage of the whole number of cases. Also the rarification of the bone trabeculæ described by *Schüller* is not characteristic for a withstood tetany, for we have found them in individuals who have not had tetany. Also experimental experiences speak against a direct connection between rachitis and tetany. *Iselin* observed remaining behind in growth in parathyroidectomized rats; and similar observations have been made by *Jeandelize*, *Moussu* and *Vassale* and *Generali* on other species of animals. *Iselin's* animals remained well proportioned, however, and showed no bone perversions.

I would also decline to subscribe to the doctrine of a connection between tetany and osteomalacia. The number of cases in which the diseases coexisted is not large. *Blačičeck*, *Weber E. Freund*, *Schultze*, *Hecker*, have reported such cases. An exception in this respect is only the noticeable observation of *Krajewska* from Bosnia; she found tetany present among one hundred fifty cases of osteomalacia no fewer than forty-eight times. All forty-eight cases affected puerperal women.

Hence there may be regarded as the symptom belonging to chronic tetany at most the rarification of the bone trabeculæ and the atrophy. It is shown by the statistics of late years that a chronic tetany existing from earliest youth may damage the development of the entire body. Disturbances of the development of speech and of the intelligence are especially frequent (see prognosis). The development of the sexual glands does not appear to suffer; in isolated cases we can find at least no remaining behind in sexual development although tetany spasms may have existed for years, from early youth or from just at the time of puberty.

The symptomatology of tetany would be incomplete were I to neglect to mention a series of symptoms that depend on a *functional disturbance of other ductless glands*, but are very frequently combined with tetany.

As has already been mentioned, *Kocher* states that after total extirpation of the thyroid in human beings, there occur in individuals in whom the symptoms of tetany predominate, marked pigmentations progressing as far as bronzed skin. Probably in such chronic cachectic conditions there is a reduction in the activity of the *chromaffin tissue*. Oftenest occur symptoms that depend on an alteration of thyroid function. Not so very rare in chronic tetany are symptoms of myxedema. *v. Frankl-Hochwart*, in looking over his cases, found symptoms of myxedema as many as thirteen times among twenty-six cases. We saw this alteration once. These myxedematous alterations of the skin occurring in chronic tetany should not be confused with the puffiness of the face previously described, or with the edema of the backs of the hands that occurs in the acute stage, which phenomena are properly regarded as angiospastic.

*Kahn* and *I* have reported an observation, that in the clinical sense is not of less significance. In a series of our own cases we saw develop in the acute stage or immediately at its close, a slight hyperthyrosis. Especially did it consist in tachycardia, headache, slight rise of temperature, increase in blood-pressure, sweats, slight tremor, and slight diffuse enlargement of the thyroid. The connection between our observations and those of *Frankl-Hochwart* is perhaps this: that in many cases of tetany at the conclusion of the acute stage or during an acute exacerbation there occurs an increase of thyroid activity and even an appreciable enlargement of the thyroid gland, and this is succeeded, in the stage of chronic tetany, by a slight degree of thyroid insufficiency (see the idiopathic form of tetany below).

## Pathogenesis of Tetany

It seems to me suitable first to set forth in detail the pathogenesis of parathyroprivic tetany; and then later in the exposition of the individual forms of tetany, to speak of their etiology separately.

As I have already mentioned at the beginning, to-day we may regard as established that experimental tetany depends on the loss or marked damaging of the parathyroid glands. This holds good for all species of animals. The course of tetany in different animals is, however, different. In some after total extirpation of all the parathyroids there occurs an acute tetany that after a short time leads to death. In others, for instance in monkeys, the course is chronic. Does the complete loss of parathyroid glands lead to tetany always?

Here is to be mentioned that all authors are agreed that older animals resist the operative attack more readily than young ones. Important in this respect are the investigations of *Iselin* who found that the young of partially parathyroidectomized rats are especially sensitive to the extirpation of the parathyroids, and die in a few hours with fulminating epileptiform seizures. Moreover, there are numerous statements that the simultaneous extirpation of thyroid gland and parathyroids is better borne than isolated parathyroidectomy. Many hypotheses have been advanced to explain this fact, a fact that our own investigations fully substantiate. The most natural of these seems to me to be the conception that on the simultaneous extirpation of the thyroid glands the metabolism and with it the excitability of the entire nervous system is reduced, and the function of the parathyroid glands is then reduced in its action. On the other hand, we know that procedures of the most diverse kinds and conditions that make great demands on the nervous system accelerate the outbreak of tetany or allow latent forms to pass over into the acute forms. If we here recognize too that the influences that may modify the course and acuity of the process may be manifold, we may well assume that the complete loss of all parathyroids leads to death in all species of animals, under the manifestations of an acute or more chronic tetany, hence that the loss of the parathyroid function is incompatible with the long continuation of life. I would not off-hand relinquish this assumption on account of the quite isolated contrary statements. *Haberfeld* and *Schilder* state that rabbits in which at first the four parathyroids are removed, and later the thymus gland with the accessory thyroid, continue to live. Continuous serial sections show the absence of any parathyroid tissue. *Wiener* even asserts that of forty-five parathyroidectomized animals, 20 per cent. did not show any manifestations of tetany. In my own numerous experiments on dogs, cats and rabbits, I have never seen an animal survive. The unconditional importance of the function of parathyroids for life is also held by *Biedl*, *Hagenbach*, and *others*. As long, however, as no further statements as to this question exist, I would leave the possibility still open that in the experiments of *Haberfeld* and *Schilder* and *Wiener* that have been mentioned, accessory thyroids escaped demonstration.

As regards the mechanism of parathyroid function, numerous opinions have been promulgated. In the foreground stands the views as to the detoxicating function. The parathyroids would seem to furnish to the blood-path a hormone which renders innocuous poisons that exist in the body. Originally the thyroid gland was looked upon as the organ preparing the poison (*Vassale* and *Generali*). Late *Pineles*, *Pfeiffer* and *Meyer*, *Oni* and *Beste*, *Berkeley* and *Beebe*, and the most recently, especially *Wiener*, have turned attention from the thyroid and have assumed that in the bodies of animals with tetany there circulates a specific poison or one originating otherwise in metabolic processes.

It is impossible for me to enter intimately into the numerous experiments that have been instituted for the establishment of the hypothesis. I would mention only the most important. *Pfeiffer* and *Meyer* state that in the sera of seventeen tetanic dogs in the death agony, they have found in six a toxic principle which injured partially parathyroidectomized mice, while the sera of normal dogs were inactive. The fact that animals with tetany are very sensitive to the various procedures affords to these experiments a great scepsis. *Ceni* and *Besta* have tried to obtain an immune serum, injecting the serum of totally ectomized dogs into rabbits and goats, and reinjecting the sera of these into the tetanic dogs. Almost regularly they cured the acute manifestations, although none of the animals remained alive. *H. Wiener* followed a similar course for experimentation, except that he used cats both for immunization and for treatment. In some animals (not all) he succeeded in combating the tetanic symptoms permanently. The residual thyroid glands of these animals were examined and found to contain no piece of parathyroid tissue. The assumption of *Wiener* that in cats there are no accessory parathyroids must in consideration of the importance of such experiments first be shown by painstaking investigations. The doubt is increased by the statement of *Wiener* that in some experiments also the injection of entirely normal serum permanently set aside the tetanic symptoms.

Although up to the present, the detoxication theory of tetany cannot be refuted, it does not seem to me to have been satisfactory. The assumption of a detoxicating function has up to the present played a great rôle in the pathology of all the ductless glands. However, it seems to me that up to the present there does not exist a single fact that strictly demonstrates this supposition. As with the other ductless glands, so with the parathyroids, another supposition seems plausible, a supposition that was first by *Rudinger* and *myself* and then further developed, with modifications, by *Kahn* and *myself*.

The cardinal symptoms of tetany depend on increased excitability or abnormal conditions of irritability of the nervous system. As to the seat of the abnormal irritability we may say the following: *Schiff* had already shown that in tetany tremors and spasms ceased after the section of the peripheral nerves. *Rudinger* and *I* have repeated these experiments, and have modified them in various ways. When we had extirpated the parathyroids in cats and at the same time had cut the sciatic nerve, immediately below its exit from the pelvis, no hyperexcitability made its appearance in the nerve peripherally from the site of the section; much more did the nerve gradually become excitable to the galvanic current in about the same time as after the section in normal animals.[1] If, however, we first obtain our tetany through parathyroidectomy and then transect the nerve when it had already become hyperexcitable, we find that the hyperexcitability continues for some time and then only gradually passes through a period of normal irritability (with normal electrical reaction) into the condition of nonexcitability. In some experiments it takes nine days before this condition is reached. From this, in reliance on former experiments of *Fröhlich* and *Löwi* on nerve-muscle preparations of the octopod Eledona moschata, we have concluded that under normal circumstances the nerve is supplied [loaded, stored, ausladen] from its trophic center, the ganglion-cell, with an as yet unknown, indefinite substance, and that separation from this center is followed by a gradual loss of this supply and by degeneration, and that in tetany there exists an abnormally high loading of the ganglion-cell or of whole neuron proceeding from it. *Biedl* had set forward to this experiment the objection that pressure on the nerve below the point of severance can no longer elicit muscular spasm. According to *Schlesinger's* explanation of *Trousseau's* phenomenon, however (reflex-process on account of irritation of sensory nerves), nothing else than this is to be expected. That, moreover, no muscular spasm appears any longer in the extremity in question is not remarkable, as every new impulse from the ganglion-cell, which is always storing anew, is lacking.

Further investigations have shown moreover that an association of the ganglion-cells of the spinal cord with higher centers is not necessary to render possible in tetany or to obtain in it the abnormal loading of the ganglion-cells. Already *Munk* had stated that after transection of the spinal cord the spasms in the paralyzed hind-extremity persisted, and *Horsley* and *Lanz* have since ascertained that after extirpation of the cortical motor areas on one side, the tetany may persist on the other half of the body.

Our own investigations showed that after section of the spinal cord in animals suffering with tetany the hyperexcitability in the paralyzed hind extremities remained exactly as in the fore extremities until death. *Biedl's* statement that there appeared in the paralyzed extremities lightning-like contractions and fibrillary muscular twitchings, but that all traces of a toxic rigidity were absent, are in direct contradiction to *Munk's* statement and our own. In addition we could most definitely assure ourselves that we saw in the paralyzed extremities, in certain cases, in cats and dogs, after complete section of the spinal cord, the occurrence of most intensive spasms in the paralyzed extremities in the acute attack. Moreover the occurrence of such spasms was not at all necessary. The exact demonstration of the galvanic hyperexcitability of the nerves of the posterior extremities, which develop even when the transection of the spinal cord has been done at the same time with the extirpation of the parathyroids, shows with certainty that *the cause of the tetanic changes lies in the ganglion-cells of the spinal cord, and not, as MacCallum and Biedl believe, in the higher centers.* By this we do not mean to assert that in tetany the higher centers do not likewise share in the condition of hyperexcitability and that the course of the twitchings in the tetanic attack may not under circumstances be concomitantly influenced by the centers that lie higher.

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[1] In more recent investigations *MacCallum* (Journal of the American Medical Association, 19, 1912, p. 319) found that the peripheral part of the nerve also becomes hyperexcitable, if it had been cut off before the parathyroid had been excised. I cannot state off-hand the explanation for the divergence of our observations.

Just as the motor nerves maintain their hyperexcitability, we may assume also that the same is true of the sensory and vegetative nerves. It is very probable that the neurons of different orders become involved in a definite sequence. In the slight grades of human tetany it is especially the neurons of the first order that are affected. Here the occurrence of, as a rule, bilateral spasms, convulsions, and pains, points to the spinal cord or to the medulla oblongata as the seat of the affection. In the acute stage the vegetative nervous system is also affected concomitantly. In the severe cases phenomena tend to occur that point to involvement of still higher centers. Forced movements point to the mid-brain, disturbances of equilibrium to the cerebellum, epileptiform convulsions to participation of the motor cortical areas, and psychoses that of the cortex in general. A similar train of thought was followed by *de Quervain* in 1893, and later by *Ast*, and *others*. In children we actually find, with increasing intensity, a mounting from cord to cerebrum. Here, as *Escherich* emphasizes, the higher centers are more frequently and more strongly involved. The retrogression of the condition tends to follow a reversed series of involvements.

Here I quote verbatim the conclusions arrived at in the work of *Kahn* and *myself*. "In tetany there exists an abnormal irritability of the motor, sensory, special sensory, and vegetative ganglion-cells that from here as a starting-point involves the entire neuron. It is principally the peripheral neurons that are found in this state of hyperirritability. Neurons of higher orders may, however, be concomitantly involved. This abnormal state expresses itself chiefly in a heightened excitability to mechanical, electrical, or chemical irritants (latent tetany). Nevertheless the abnormal tension in the ganglion-cell, either per se or through any other occasioning factor, may lead to a heightened irritability in the organs supplied by it, and may become manifest in tonic spasms and fibrillary twitchings of the transversely striated muscles, in paresthesias, in tonic contractures of the smooth muscles, in heightened secretional processes, etc.

"Thereby is found a partial unloading of the ganglion-cells, although apparently not in very great degree, so that the hyperexcitability is still present after the attack. This conception explains why at one time an occasioning factor may call forth a spasm, while a short time afterward it is inactive, perhaps becoming active again on the next day, and why the spontaneous condition of hyperirritability in tetanics is subject to such significant rapid change. This behavior may be observed especially beautifully on animals that have been parathyroidectomized; these dogs and cats may be the victims of the most severe spasms, and yet a few hours later may play as vivaciously as ever. Only the exact investigation of the electrical and mechanical hyperexcitability now affords knowledge as to the latent tetanic condition. This view also makes appear intelligible the fact that certain nerve territories that have immediately met with numerous irritations (peripheral neurons) are especially preferred, and that the conditions of irritability in the different nerve territories are of different strengths, and may be subject to considerable change.

"In what relation do the parathyroids stand to the hyperexcitability or to the condition of excitability of the ganglion-cells. 'Everywhere where excitation is, is also present inhibition' (*Meltzer*). According to *Bechterew*, the inhibitory processes are to be regarded as an indispensable protective arrangement of the central nervous system. The normal condition of irritability of the ganglion cells is guaranteed only by the finest regulation of increase of activity [Förderung] and inhibition. *Falta* and *Rudinger* have expressed the opinion that the epithelial bodies exercise inhibitory influences on the ganglia by a hormone and that the diminution or complete withdrawal of this inhibition leads to an abnormal loading of the cell with energy.

"We do not know anything more intimately as to the action of this hormone. It is impossible, however, to bring this hypothesis in the combination with that developed by *MacCallum* and *Vöglin*, by our following the assumption of these authors that the parathyroid glands influence the calcium metabolism in the central nervous system by means of a hormone. The hormone of the parathyroid glands might thus be regarded as an assimilatory hormone, with the withdrawal of which there occurs loss of calcium in the ganglion-cells and hyperirritability of the same."

The details up to the present confine themselves to the mechanism by which insufficiency of the parathyroids leads to tetany; they set forth that all forms of tetany depend on an absolute or at least a relative insufficiency of the parathyroids. The different causes of parathyroid insufficiency will be discussed later, with the exposition of the different forms of tetany and the pathological anatomy.

We shall add a few words as to the relation of myotonia, epilepsy and eclampsia to tetany. The occurrence in tetany of symptoms similar to those of myotonia is, as already mentioned, not rare. The fact that they are also observed in experimental tetany, ensures this membership to tetany. The intention spasms may be explained by the fact that the will impulse furnishes the determining factor for a tetanic spasm. In addition there often occurs however pitting on percussion and the myotonic electrical reaction. On the other hand there occur true cases of myotonic congenita to which are superadded the clinical picture of tetany.

In these cases, as *v. Orzechowski* points out, the symptoms of tetany are only of a slight grade; with the decline of the tetany, the myotonia remains. This coincidence of tetany and myotonia has been sufficient for *Lundburg* and *others* to ascribe the cause of myotonia to an insufficiency of the parathyroids. The assumption seems to me to be fully unsubstantiated, as in true myotonia all symptoms that according to experimental experiences we have come to regard as the cardinal symptoms of parathyroid insufficiency, are absent. Myotonia is an affection of the muscles (*Erb*, *Schultze* and *Schieffendecker* and *others*). The occurrence of symptoms similar to those of myotonia in tetany perhaps find its explanation in a definite alteration of the metabolism. It is remarkable that just those animals in whom the thyroids and parathyroids have been removed show these manifestations. Further worthy of notice is a case of *Hoffmann's* in whom the myotonic symptoms disappeared on the administration of thyroid gland and in whom they reappeared after withdrawal of the treatment, while the tetanic symptoms were not essentially affected. Perhaps there is a certain relation between this condition and the high-grade mechanical hyperexcitability of the muscles such as is not rarely seen in cachectic conditions.

As for epilepsy, it has already been mentioned in the consideration of the symptomatology that tetany may develop on an epilepsy that has lasted for a long time, that also tetany and epilepsy may develop simultaneously in individuals not previously epileptic, and indeed may improve simultaneously. In many cases the epileptic convulsions occurring in severe tetanic attacks may remain the sole manifestation of epilepsy. It should further be mentioned that *Chvostek's* phenomenon is not rarely elicitable in epileptics and that *Fleischmann* and *Poetzl* as reported by *Redlich* found twenty-eight times defects of the enamel among sixty epileptics, a fact that perhaps indicates that individuals who in early years have passed through tetany, later often become epileptics. Most important for the relationship between tetany and epilepsy are the cases of parathyroprivic tetany with epilepsy. *Redlich* has collected twenty such cases from the literature and adds a case of his own. The frequent coincidence of tetany and epilepsy shows that this combination is "no accidental happening" (*v. Frankl-Hochwart*, *Schultze*, *Redlich*). As to the intimate connection we really know nothing certain. *Westphal* supposed that tetany and epilepsy depended on the same toxic cause, which, as *Chvostek* later elaborated, led both to alterations in the central nervous system and to functional disturbances of the epithelial bodies. *Pineles* supposed that the toxin of tetany produced a latent predisposition to epilepsy; *Curschmann* that it increased the excitability of the cortex and subcortex. Experimental pathology has as yet furnished no reliable evidence. In a cat in which *Kreidl* extirpated three parathyroids, epileptic attacks occurred regularly on operations on different parts of the cortex. *Redlich* could not confirm the results of this experiment when he repeated it. Only in one experiment an operation on the brain cortex after total thyroparathyroidectomy, did he find severe tetanic and severe epileptic attacks occur simultaneously.

Attempts have also been made to refer epilepsy without tetany to an insufficiency of the parathyroids. As was to have been expected, pathological anatomy did not substantiate this hypothesis. *Erdheim* examined the parathyroid glands in two cases of status epilepticus; in one they were entirely normal and in the other they were slightly sclerotic. Also *Claude* and *Schmiergeld* in thirteen cases found no constant tissue of change.

Also the relationship of tetany to eclampsia has not been cleared up in a manner that is satisfactory. In the years of childhood tetany may occur under the guise of eclamptic attacks, as has been mentioned already. It has been held that children who have suffered with eclampsia, later became epileptic. *Birk* could not find this in his material, to which are opposed the statements of *Potpetschnigg*. The eclampsia of adults is as a rule to be separated from tetany, in that in eclampsia the cardinal symptom of parathyroid insufficiency, the galvanic excitability is absent. *Erdheim* could not corroborate the statements of *Pepere* and *Zanfrognini*, who found a lessened number of parathyroid glands in their cases of eclampsia. In four cases of eclampsia examined by *Erdheim* the parathyroids were normal except for the fact that they were very hyperemic and were permeated with small hemorrhages, which manifestations are certainly regarded as secondary.

## FORMS OF TETANY AND PATHOLOGICAL ANATOMY

### 1. The Parathyroprivic or Traumatic Tetany

It was first noticed by *Nathan Weiss* that in *Billroth's* clinic the extirpation of the thyroid gland was often followed by tetany. Since that time the literature as to this subject has grown enormously. The question is handled with especial thoroughness in the publications of *v. Eiselsberg* and *Kocher*. *v. Eiselsberg* in his "Diseases of the Thyroid Gland" publishes a classic description of tetany after extirpation of the thyroid gland. In Vienna tetania "strumipriva" was observed much more frequently than in Bern. Among forty cases of total extirpation of the thyroid gland, tetany was seen by *Kocher* only nine times, of which number only three were pronounced cases; among thirty cases of partial extirpation only six were acute tetany; among ninety-seven operations in Basedow's disease, only 5 were tetany; one case of ligation of all four arteries supplying the thyroid gland led to peracute tetany. Epileptiform tetany has been observed by *v. Eiselsberg*, *Kocher*, and *others*, in the wake of partial extirpation. Originally tetany was attributed to the failure of the thyroid gland. With the awakening knowledge of the significance of the parathyroid function were heard loud voices referring thyroid-gland tetany to the simultaneous damaging or removal of the parathyroids. Fundamental for this view are the investigations of *Pineles*, and of *Erdheim*. The latter observed three cases that had died of more or less acute tetany after strumectomy. In the first case, which had shown a more chronic course, the entire throat portion was cut in the serial sections; it was found that all four parathyroids were missing, although two small accessory parathyroids were found in the midst of the thymus tissue. In both the other cases, that which had pursued an acute course, parathyroids capable of functionating were not to be found. *Erdheim* pointed out that the great frequency of strumiprivic tetany in Vienna had its explanation in the fact that there the operations on the thyroid gland were conducted according to the old methods, while *Mikulicz's* wedge resection or *Kocher's* resection enucleation are the rather adapted to avoid the parathyroids. However, the genius loci must not be entirely overlooked in the explanation of the fact. To-day, when we are well informed as to the significance and topography of the parathyroids, tetany after operations belongs to the greatest of rarities. A preparatory search for the parathyroids is not necessary; sufficient is the adherence to the propositiva of *Pineles* and *Erdheim* to let remain both the lower lobes; search for the parathyroids is directly indicated only when it becomes necessary to remove the entire thyroid gland, in malignant struma. *v. Eiselsberg* has reported a case in which the greater part of the thyroid gland was removed for malignant adenoma. Myxedema developed, and retrogressed after the appearance of metastases in the sternum. Extirpation of these metastases (healing by secondary intention) was followed by a recurrence of the myxedematous symptoms and by tetany. *Erdheim* explains this case in that at the first operation there was left behind one of the lower chief parathyroids, and that this became sacrificed at the second operation.

The etiology of the thyroprivic tetany is thus clear. This form of tetany depends on the loss or the damaging of the parathyroids at the operation.

*Proescher* and *Diller* report a case of *traumatic* tetany in the adult. A young man developed typical tetany eight days after a severe blow. At autopsy there were found numerous small fresh hemorrhages in parathyroids, that were in addition hypoplastic. Belonging to traumatic tetany are also numerous cases of the tetany of sucklings, as we shall see later in the section on tetany in children.

## 2. Tetany in Diseases of the Thyroid Gland

Cases of tetany in myxedema are rare. They are strikingly frequent, combined with epilepsy (cases of *Stewart, Schönborn*, and *myself*).

Cases of thyroiditis with tetany were observed by *v. Eiselsberg* and *Kocher*. Although there are no pathologico-anatomical investigations yet it may readily be supposed that acute inflammatory or sclerosing processes that attack the thyroid also involve the parathyroid in sympathy. In strumous degeneration of the thyroid gland the parathyroids associated with the capsule may become involved and thus brought to atrophy. Such cases have been reported by *Steinlechner, Fraisseix, Hirschl, Marinesco, Jacobi* and *others*. I shall speak in the consideration of idiopathic tetany of the triad described by *v. Frankl-Hochwart*—tachycardia, tremor, and *Chvostek's* symptoms (II and III), with struma and vasomotor excitability. This condition was called "tetanoid" by *v. Frankl-Hochwart* (see above for the consideration of the hyperthyrosis or hypothyrosis in tetany).

## 3. Tetany in Infectious Diseases and Intoxications

Tetany has been observed in the most diverse infectious diseases. Most quoted is the frequent association of tetany in epidemics of typhoid fever (*Aran* and *Rabaud*). Tetany has also been observed in angina, influenza, acute articular rheumatism, croupous pneumonia, and many other infectious diseases. For the most part these cases occur in places where tetany is common and during the time of the occurrence of tetany. Therefore it is very probable that in the majority of these cases the infectious disease constitutes only the determining factor, that no form sui generis is present, but that these cases belong to the idiopathic tetany to be described later. At all events it is not improbable that a generalized infectious process would affect also the parathyroids, and lead to infiltration or at least to parenchymatous degeneration of these organs, thus temporarily deranging their function.

In this category belong the cases of tuberculosis of the parathyroids. There have been already published numerous statements as to the occurrence of this condition (*Benjamin, Carnot* and *Delion, Pepere, Königstein, Stumme, Schmorl* and *Eggers*). *Carnot* and *Delion*, and *Pepere*, observed typical tetanic symptoms in phthisis, in the days immediately preceding death. *Stumme* observed *Chvostek's* phenomenon. These findings are certainly interesting in consideration of the frequent occurrence of *Chvostek's* phenomenon in tuberculosis, as mentioned previously.

We can regard the cases that occur in poisonings as a less independent group. The most diverse poisons, such as ergotin, phosphorus, carbonic oxide, spermin (*Oppenheim*), lead, morphine, chloroform, etc., may lead to an outbreak of tetany. The assumption that the poisoning constitutes only the determining factor has a firm basis in the investigations of *Rudinger. Rudinger* first determined that in cats the peroral administration of calomel, the subcutaneous administration of morphine, atropine, tuberculin and ergotin, and the inhalation of ether does not influence in any way the electrical excitability. After these animals had been placed in the condition of latent tetany by a partial parathyroidectomy, the administration of these poisons led to spasms.

### 4. Idiopathic Tetany (Occupation Tetany)

In the description of this form I chiefly follow the exposition of *v. Frankl-Hochwart.* Idiopathic tetany shows the characteristic that it chiefly occurs in persons following certain occupations, that it is especially frequent in certain localities, and that it shows an epidemic-like increase during certain months. The last observation was first made by *N. Weiss* and *v. Jaksch.* The statistics of *v. Frankl-Hochwart* from the years 1880 to 1905 embrace five-hundred seventy-six cases (among which, however, only five hundred twenty-eight were cases of occupation tetany). Of these occurred in

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Jan. | 66 | Apr. | 111 | July | 12 | Oct. | 10 |
| Feb. | 88 | May | 52 | Aug. | 9 | Nov. | 15 |
| Mar. | 137 | June | 36 | Sept. | 9 | Dec. | 31 cases |

The especial predisposition of the followers of various occupations was first mentioned by *v. Murdock*, later by *von Jacksch, Mader, Hoffmann, Schultze*, and *others.* It is especially cobblers and tailors that become affected with tetany. Among five hundred twenty-eight cases of *v. Frankl-Hochwart* were two hundred twenty-three cobblers, one hundred seventeen tailors, thirty-eight carpenters, thirty locksmiths, thirty turners and the remainder were divided among the other occupational classes. In women, it is especially the maids [*i.e.*, lady's maids] that become affected (thirty-two of ninety-nine female cases). Also soldiers become affected with it not at all rarely (*Mattauschek*).

Another characteristic of occupation tetany is as has already been mentioned that it prefers certain cities. It is most frequent in Vienna, Heidelberg, and is not rare in Budapest; it is, however, especially the lead workers who become its victims (*Jakobi*). Moreover, its epidemic extension presents variations. For instance it was very frequent in Paris in the years 1830-1860. Since that time it has been very rare there. In Heidelberg also according to the most recent statement of *Schönborn* has it become rarer. In the other cities that now harbor it, it shows a large increase in certain years. Thus *Mattauschek* observed an epidemic among soldiers of the Vienna garrison in the year 1896. Outside these cities, tetany is sporadic nearly all over. In several places, small endemics have been observed.

Idiopathic tetany shows a great inclination for relapses. After the first attack it passes over in the latent stage, and tends to recur the next year at the time for tetany (acute relapsing form of tetany, *v. Jaksch*). There is in addition a chronic form in which the disease never entirely disappears. The first form may pass over in the latter (see prognosis).

Concerning the *etiology* of idiopathic tetany we know nothing that is certain. The endemic-epidemic occurrence, as is intelligible, has a priori given occasion to the thought of an infection. This is supported by the increase in temperature that occurs in the acute stages; I mentioned before that this is rather due to disturbances in the regulation of heat, which may serve as a partial manifestation of the irritable condition of the vegetative nervous system; it may be said it occurs to a much greater degree after parathyroidectomy. Recently *A. Fuchs* has pointed out the resemblance of the clinical pictures of tetany and ergotism (typical form of spasms, paresthesias, trophic disturbances, cataract formation, epilepsy, psychoses, etc.), and is inclined to refer occupation tetany to poisoning with bad corn. *Biedl* comments on this hypothesis, stating that there is formed in the putrefaction of histidin an amino-base (imidoazolyethylamin) that is identical with the active agent in ergotin. I shall assume an expectant attitude with regard to *Fuch's* hypothesis, considering that more facts are not at our command.

Very important for the etiology of idiopathic tetany appears to me a contribution by *McCarrison*. In certain valleys among the Himalaya mountains exists much epidemic tetany and indeed just in those places where there is epidemic goiter. The disease affects most solely women, and the only man in whom *McCarrison* observed it was not affected with goiter. The epidemic of tetany takes on in numbers in spring, as with us, and is increased during pregnancy and lactation. The goiter that predominates in this locality is of a marked degenerative character. Numerous cases of tetany observed show also signs of an incomplete myxedema; very noteworthy is also the statement that persons that suffer from tetany become free of this affection when they go into tetany-free districts, and finally reacquire the tetany when they return to the original spot. In the light of this observation seems to me most important the fact that our localities for tetany, Vienna and Heidelberg, show an especial form of goiter in the clinical sense, and further the fact already mentioned that *v. Frankl-Hochwart* has observed that a great number of cases of tetany later show distinct symptoms of myxedema, and finally the fact that *Kahn* and *I* have described the observation that manifestations of a slight hyperthyrosis and thyroid swelling can develop in the acute stage, or immediately at the close of the acute stage. As tetany is not frequent throughout in any goiter districts—in Steiermark and Tyrol it practically is absent, and in Switzerland very rare—we may suppose that not every goiter noxus may bring about idiopathic tetany, but an especial goiter noxus or a noxus that is similar to the goiter noxus. But even such an assumption is, as I fully know, not satisfactory in certain directions. It does not explain why tetany is so frequent in the springtime nor why certain occupations are preferred in such a striking manner. I believe moreover that it would be worth while to pursue the problem further.

## 5. The Tetany of Children

The tetany of children is characterized by its great multiformity of manifestations. The assumption of the collectivity of these manifestations is of recent date. In 1887 *Cheadle* had already stated that laryngospasm, tetany, and convulsions were only the varying expression of the same "constitutional morbid state." Since the year 1890 *Escherich* and *v. Wagner, Ganghofner* and later especially the school of *Escherich* maintained the teaching of the belonging together of laryngospasm and the eclampsia of childhood, and, in spite of much opposition, have held to these doctrines, by the demonstration of the increased electrical excitability and the delimitation from similar manifestations of another kind. The pathologico-anatomical investigations of *Erdheim* and *Yanasse* seem adapted for establishing this view on a safe basis. Tetany of early childhood occurs chiefly in the third to the twentieth month of life. This is the form that deviates from the clinical picture of tetany of adults through the multiplicity of its manifestations. The tetany that sets in from the third year of life on is essentially similar to the tetany of adults. The tetany of sucklings which often manifests itself only through increased galvanic, and especially anodic, hyperexcitability is extraordinarily frequent in rachitic children and especially also in children that have been fed artificially. This occurs almost always in the cold time of the year. It shows a preference, as does rachitis, for northern countries especially, but is distinguished from the tetany of adults by its uniform extension.

The investigations of *Erdheim* and *Yanasse*, already mentioned, have furnished an interesting elucidation for the etiology of this form of tetany. Already in 1903 *Erdheim* had mentioned the finding of hemorrhage in the parathyroids of new-born children, and in 1906 he reported like findings in two of the sucklings that had died of tetany. *Yanasse* then examined systematically the parathyroids of thirty-five children who had died at the age of fifteen months. He found that in cases in which the electrical excitability had been normal during life, the parathyroids were normal. In those children, however, in whom there had existed electrical hyperexcitability, he found almost constantly hemorrhages or the remains of hemorrhages (in 71 of the 104 cases investigated). The hemorrhages are demonstrable at about the twelfth month, and are very probably to be referred to trauma during birth. According to the later investigations of *Haberfeld*, the damaging influence of the hemorrhages does not act so much on the destruction of the parathyroid parenchyma as on the inhibition in growth of these organs conditioned by it. *Erdheim* and his collaborators, on the basis of their investigations, adhere to the view that the tetania infantum depends on a hypoparathyroidism and that the artificial nourishment constitutes only the occasioning factor. *Erdheim* is corroborated by *Peters, Schmorl, v. Verebely* and *Strada. Auerbach, Grosser* and *Betke, Bliss, Raymond, Jörgensen* and *others* have pronounced against the assumptions on the ground of pathologico-anatomical investigations. Thus *Escherich's* views in their universal form are to-day not generally shared.

*Heubner* has grouped together the diseases mentioned under the less prejudicial name of spasmophilic diathesis.

The etiology of the tetany of later childhood (puerile tetany according to *Escherich*) is as yet unknown; perhaps it is identical with that of the idiopathic form.

## 6. The Tetany of Maternity

Under this heading we understand the tetany observed in pregnant, child-bearing, or puerperal, women. *v. Frankl-Hochwart* has collected fifty-three certain cases from the literature, and adds to them twenty-three of his own. Of these twenty-eight affected women who were pregnant, nineteen occurred after the delivery, and twenty-nine during the puerperium. The beginning of tetany in pregnant women occurs in the sixth to the eighth month [of pregnancy].

To-day maternity tetany can scarcely make a bid for the distinction of a form sui generis. A portion of the cases belong in the group of tetany after strumectomy, the rest in great part to the group of idiopathic tetany; these come from places affected with tetany and occur especially in the tetany months, and it seems to me noteworthy that there do occur epidemics chiefly in the form of maternity tetany. While for example, according to the summary of *Adler* and *Thaler*, maternity tetany is relatively rare in Vienna (at the first gynecological clinic at Vienna only nine cases of the tetany of maternity were observed among about 30,000 cases); a great number of the cases described by *Krajewska* and also by *MacCarrison* belong to this group. In all the forms the pregnancy or lactation plays the rôle of the determining factor only. This has been established by numerous experiments on animals. At first *Horsley*, later *Vassale, Pineles, Erdheim* and especially *Adler* and *Thaler* showed that in partially ectomized animals that show no signs of tetany, the tetany comes to expression with the progress of the pregnancy. In cases of slight parathyroid insufficiency, this may occur only in the course of the second pregnancy, or, as has repeatedly been observed, there may even occur a normal pregnancy interpolated between pregnancies complicated with tetany. A very interesting case of this sort is reported by *Meinert*. In this case there had been two births that were normal, then in the third there was tetany; then there were two more normal births, to be succeeded by a sixth pregnancy in which the tetany recurred. A strikingly marked atony of the uterus has been observed after the delivery in women who have tetany (cases of *Erdheim* and of *Neumann*). The tetany during pregnancy tends to have a very unfavorable influence on the fetus. The birth of macerated fetuses has been reported several times (*Pick*, *Neumann*); or the statements are that the children indeed were delivered, but soon died in convulsions (*Kocher*, *v. Frankl-Hochwart*). These last statements are very important with respect to the investigations of *Iselin*.

The question as to why pregnancy calls forth tetany in predisposed individuals is not as yet fully explained. We may readily conceive that pregnancy makes increased demands on all the ductless glands and thus unmasks a latent insufficiency. Perhaps similar relations are to be found with respect to tetany combined with *osteomalacia*. In osteomalacia, *Erdheim* found hyperplasia of the parathyroids. He assumes that in osteomalacia there are especial demands made on these glands. The statement of *Erdheim* has been often corroborated. *Schmorl* found the parathyroids normal in four cases of rickets, but in a case of osteomalacia the parathyroids were markedly hypoplastic. In three other cases the parathyroids were normal, although *Erdheim* points out that the islands were not examined with the use of the osmium stain. *Strada* found the parathyroids enlarged in a case of osteomalacia, and unaltered in two cases; in one case *Bauer* found in one parathyroid an adenoma, and foci of proliferation in three others. Finally the parathyroids of twenty-four individuals were examined by *Todyo*. He found hyperplastic processes as described by *Erdheim* four times. In seven cases of osteomalacia they were, however, absent only once, and in six cases only one parathyroid was examined. In eleven cases of senile osteoporosis he found, on the contrary, hypoplasia eight times.

## 7. Tetany in Gastrointestinal Diseases

Tetany is observed in the most diverse gastric and intestinal affections. I mention only acute dyspepsia, acute and chronic enteritides and helminthiasis. Especially are those cases brought into relief in which on account of some obstruction there occurred a dilatation of the stomach, or (in rare cases) a dilatation of the intestine, and a stagnation of the gastric and intestinal contents. From the great group of gastrointestinal tetany a number of cases are to be singled out in which the gastrointestinal disturbances constitute only one symptom of the tetany. I would agree with *Chvostek* that these cases are not at all rare. This has been taken up in detail in the consideration of the symptomatology. In a further group of cases an indisposition of the stomach or intestines may constitute the determining factor for the tetany.

An especial interest attaches to that form which occurs when the gastric or intestinal disturbance has existed for a long time. Attention to this form was directed first by *Kussmaul*. Since that time there have been published numerous reports concerning it (*Fleiner, Fr. Müller, Gerhardt, Bouveret* and *Devic, Ewald, Albu, Schlesinger, v. Frankl-Hochwart, Rudinger* and *Jonas, Wirth*). The most various conditions have been found: Cicatrized ulcer of the pylorus or the duodenum, hour-glass stomach, malignant processes (such as carcinoma or sarcoma) in the neighborhood of the pylorus, or tumors of the gall-bladder or of the pancreas that lead to stenosis, torsion of the stomach, acute paralytic dilatation of the upper small intestines, in children dilatation of the colon, etc.

There has also been reported a group of cases of dilatation of the stomach without demonstrable stenosis. I mention from the newer literature only the cases of *Ferrannini* and of *Fleiner*.

The tetany that occurs in all these conditions may be quite rudimentary. Not rarely, however, it is of the most severe forms, forms that are attended with universal spasms and loss of consciousness.

*Bouveret* and *Devic* distinguish a simple form attended with paresthesia and typical spasms of the extremities, and a "tetanisme plus ou moin généralisé," that may lead to dyspnea and death from asphyxia principally through involvement of the muscles of respiration, and a form attended with loss of consciousness and coma. These severe forms of stomach tetany leave the prognosis always somewhat doubtful. The present statistics show a mortality of about 60–70 per cent.

Numerous hypotheses have been brought forward to explain this form. In a certain number of the cases perhaps an affection of the gastrointestinal tract may play the determining rôle. This may be likely through the circumstance that, as the figures of *v. Frankl-Hochwart* show, a great number of these cases occur during the tetany months. On the grounds of this observation *Rudinger* and *Jonas* have upheld the supposition that the tetany of gastrodilatation is nothing more than tetany acquired in the course of a gastrodilatation. This explanation does not seem to me to be entirely satisfactory. Before everything else, it is striking that this form of tetany is less confined to the tetany districts. *Kussmaul* supposed that the tetany was caused by a thickening of the blood, due to the frequent vomiting and the diminished absorption of water. *Fleiner* has adopted this theory, pointing to the hyperglobulia observed by *Fr. Müller* and also himself. This hyperglobulia is, however, as we have already seen, not the cause of tetany spasms but their effect. *Gerhardt, Palliard, Ewald, Albu*, and *others* have supposed that toxic substances bring about the tetany, their origin being due to the stagnation of the gastric and intestinal contents (autointoxication theory). The finding of diamines in the stomach contents and in the urine of such patients means nothing, as they are also found there in other diseases.

It is certain, however, that in many cases, the tetany promptly disappears on combating of the stagnation (for example washing out of the stomach). The explanation of this subject has as yet received no elucidation from pathologico-anatomical investigations. *Erdheim* found the parathyroids entirely normal first in a case of severe gastric tetany, then in a second case with slight gastric manifestations, and third in the case of tetany in the course of enteritis. *MacCallum* in a case of gastric tetany found five rather large parathyroids whose cells showed abundant mitoses. This he regarded as hyperplasia. *Kinnicutt* found in a case of gastric tetany the parathyroids normal. It seems, therefore, that in a group of these cases there is present only a relative insufficiency of the function of the parathyroids with, however, markedly increased demands on them; we should consider further the possibility that in high-grade stagnation in the gastro-intestinal tract substances are formed and absorbed that increase the excitability of the nervous system so markedly that under circumstances the action of the parathyroids no longer suffice; we must also assume, however, a certain predisposition of the individuals affected, as conditions of stagnation in gastrointestinal conditions are rather frequent, while complication with tetany is very rare.

If we pass in review what has been said concerning the individual forms of tetany and their etiology, we find that we cannot deny that the view that all forms of tetany may be grouped together from the point of view of relative or absolute insufficiency of the parathyroids is, as a result of pathological anatomy, not sufficiently proved. All the rest of the pathologico-anatomical findings that up to the present have been brought into relief in tetany, findings such as alterations in the ganglion-cells of the spinal column, in the marrow or in the nerve fibers themselves, have been inconstant. As yet unelucidated as to its significance is the finding of a premature sclerosis of the fine and finest cerebral vessels, especially in the medulla of the cerebrum and in the cerebellum, such as *A. Pick* pointed out in four cases of chronic tetany.

**Differential Diagnosis.**—We distinguish an acute relapsing and an acute recurring form of tetany. We should also appropriately distinguish between a manifest and latent tetany unattended with spasms, and finally between fully developed form of the formes frustes (the expression tetanoid I regard as less to the purpose); it is the latter differentiation that is attended with differential diagnostic difficulties. In general, the diagnosis of tetany is easy, as its most important criterion, the galvanic hyperexcitability, has as yet been observed in no other condition. As has previously been mentioned, *Erb's* phenomenon may be temporarily absent even in the acute stage. In such cases great value can be attached to *Chvostek's* phenomenon only when it is present pronouncedly. If in addition there are present paresthesias in the territory of the ulnar nerve and complaints as the sensations of tension in the hands and feet, the diagnosis of tetany appears to be very likely; often there occurs in the further course of the disease fibrillary contractions, or *Trousseau's* phenomenon or only transitorially a slight degree of heightened galvanic hyperexcitability thus making entirely certain the diagnosis. Not rarely *Reichmann's* disease may be attended with quite rudimentary forms during the tetany season.

*v. Frankl-Hochwart* and *Fleiner* have regarded certain cases of gastric tetany described in the literature as spurious, as they presented only sensation of tension in the hands, but *Erb's* phenomenon was absent. During the last few years I have observed six cases of gastric tetany (see also *Falta* and *Kahn*); in almost all I was dealing with a typical *Reichmann's* disease with marked dilatation of the stomach and increased peristalsis, indeed even antiperistalsis, phenomena that retrogress in many such cases on appropriate treatment. In some galvanic hyperexcitability, mostly of a slight grade, was present quite transitorily. However, the paresthesias and the sensation of tension outlasted *Erb's* phenomenon for a long time. Therefore, in the formes frustes we may miss *Erb's* phenomenon, even on repeated examinations. With full recognition of its prominent importance for the diagnosis, there do occur, however, isolated cases in which it is absent and in which we establish the diagnosis tetany in spite of this fact.

Concerning diseases that may be confused with tetany I mention only the following: Tetanus is readily distinguished from it by the increase in reflexes, by the noninvolvement of the hands, and by the absence of the typical symptoms of tetany. Also the delimitation from meningitis, from acroparesthesia in chronic poisonings and from occupational spasms is always easy, as in these diseases the typical distinguishing symptoms of tetany are absent. Hysteria may occur combined with tetany, and in such a way that tetanic and hysterical spasms are present simultaneously, or the hysterical spasms may come to the fore on the retrogression of the tetany, or hysteria alone may exist simulating tetany (pseudotetany) (*E. Freund*, *H. Curschmann*, *F. Chvostek*). In this form naturally *Erb's* phenomenon is absent, but hysterical stigmata are present. The pseudotetanic attacks may simulate the true tetanic attacks in an illusory manner. The unilateral occurrence of the spasms would rather point to the thought of hysteria. Yet it should not be forgotten that a few true cases of hemitetany have been known (*H. Freund*, *v. Frankl-Hochwart*, *v. Jaksch*, *E. Freund*, *et al.*). Too, *Trousseau's* phenomena is often simulated illusorily. Especially to be considered is the absence of the paresthesias usually attending tetanic attacks, and of *Erb's* phenomenon, and the presence of fibrillary contractions. If these cases of pronounced hysterical symptoms are added to a true tetany, *Erb's* phenomenon is decisive.

In the differential diagnosis between epilepsy and tetany it is especially important to determine whether epileptiform convulsions belong to tetany or whether there exists a true epilepsy in addition to the tetany. Especial attention must be directed to the aura, to the incontinence of urine and feces during the attack and to the postepileptic stupor. Loss of consciousness in tetany is very rare, in epilepsy it is the principal symptom. In similar fashion a case of tetany with symptoms of myotonia must be investigated with regard to the cardinal symptoms of true myotonia (myotonic reaction).

The galvanic hyperexcitability is important, according to *Escherich*, for differentiation from eclamptic convulsion of the years of childhood.

The **prognosis** for the different clinical forms of tetany is not the same, and in strumiprivic tetany the prognosis quoad vitam may be very unfavorable. To-day such cases scarcely come into consideration. The prognosis of *idiopathic* tetany quoad sanitationem was formerly regarded as favorable. Since *v. Frankl-Hochwart* has reviewed his cases the views as to this point have changed considerably. Of fifty-five cases only nine were entirely healthy, seven showed chronic tetany, general nervousness and chronic invalidism, nineteen showed slight tetanic symptoms and trophic disturbances, six showed chronic invalidism without symptoms of tetany, eleven had died four to eleven years after the outset of the tetany. *Saiz* furnishes similar unfavorable statistics. He states that of nine cases only one remained free of distress, and also this individual had sustained a recurrence. Cases of death from *tetany of maternity* have been reported (*Trousseau*, *Schundlechner*, *Blažiček*, *et al.*). Also transition into chronic tetany has been observed. *v. Frankl-Hochwart*, *Adler*, and *Thaler* and *Novak*, in contradistinction to *Fellner*, hold therefore the prognosis as doubtful. Especially unfavorable is the prognosis in *tetania gastrica;* here it happens that the stomach affection itself frequently influences the prognosis unfavorably. Also in the tetany of childhood the revisions of the more recent period have furnished rather unfavorable results as to the length of life and especially as to the further development (*Escherich*, *Thiemich*, *Birk*, and *Potpetschnigg*).

According to *Escherich*, 25 per cent. of the nurslings at the hospitals who are sick with tetany die, and *Thiemich* and *Birk* in Breslau and *Potpetschnigg* in Graz have concerned themselves with the later fate of children who have been sick with tetany. Both statistics come to the result that a not inconsiderable number of such children soon die. Those investigated were only rarely quite normal. In the majority of cases they showed disturbances of the psychical and intellectual development and especially remaining behind in the development of speech.

The **treatment** of tetany should be concerned first of all with efforts to replace the lacking parathyroid function or to improve the insufficient parathyroid function. It is a pity that up to the present all attempts have been futile. The *substitution therapy* that was so valuable in thyroid insufficiency has in this case up to the present led to no certain result. It is intelligible to-day why the thyroid medication formerly employed in tetany was without results. It is remarkable, however, that no decisive results are obtained by the administration or subcutaneous employment of dried parathyroid gland or of extracts of parathyroids. The favorable statements of a few authors (parathyroid tablets, *Marinesco*, *Lowenthal*, *Wieprecht;* parathyroantitoxin, *Vassale*) stand in contradiction to the negative results of the exact trials of *Pineles* and the statements of many other authors.

*Pineles* found that neither stomachal, nor subcutaneous, nor intraperitoneal administration of parathyroid extract in large doses served to influence in any way parathyroprivic tetany. Also the feeding of very large amount of the extract of the parathyroids of horses, remained in human beings without results. One is reminded of the negative results of pancreas feeding (islands of *Langerhans*) in diabetes. The parathyroids are likewise no storage glands.

The attempts to transplant the parathyroids at first awakened great hopes; *v. Eiselsberg* and later *Payr* transplanted the thyroid gland in the abdominal wall or in the spleen and (on account of associated transplantation of the parathyroids) prevented the outbreak of the tetany. *Enderlen* first showed microscopically that the parathyroids transplanted with the thyroid gland remained capable of functionating, in that in part they regenerated. Since that time numerous transplantations have been undertaken by *Biedl*, *Pfeiffer* and *Meyer*, *Halstead*, *Harvey*, *Cristiani*, *Leischner*, *et al.*); favorable results have also been reported in man (first by *v. Eiselsberg*); favorable results were reported by *Pool-Kocher* (transplantation into the bone marrow) *v. Garré*, *Boese* and *Lorenz*, and *Danielsen*. The clinic of *v. Eiselsberg* later met with unfavorable results. On this account, the question was restudied by *Leischner* and *Kohler*, who concluded that the parathyroids behave quite similarly to the thyroid, that is, that only autotransplantation is attended with favorable results; while on homiotransplantation it is true that the parathyroids functionate for a time at first but later become absorbed.

The administration of **calcium salts** has been regarded by *MacCallum* and *Vögtlin* as a causal therapy. The condition of excitability in ectomized animals should become dampened. *Curschmann* reports the improvement in three cases of tetany in man; *E. Meyer* in a case of tetany of pregnancy. *Kahn* and *I* studied the excitability of the nerves at intervals of two to three hours, and, after the administration of even a large amount of calcium lactate never observed a distinct influence on the same. Also the intramuscular administration of "Kalzine" (*v. Müller* and *Saxl*) was ineffective. If the assumption that in tetany the assimilation of calcium in the nervous system is disturbed holds good, it seems to me that the negative results become intelligible; the person with tetany behaves himself against increased administration of calcium just as a patient with pancreatic diabetes behaves himself against increased administration of sugar. We should expect, on the contrary, in conditions of increased dissipation of calcium, a result from the calcium administration. Perhaps we may explain in this manner the favorable results of calcium treatment in Basedow's disease.

There therefore remains for the treatment of tetany only *symptomatic therapy*, a therapy that likewise is almost ineffective. Weak sedatives such as the bromides and valerian are especially ineffective. In severer cases we can occasionally ameliorate the condition by the use of chloral. *Levi* claims to have had good results through blood-letting, and *Narbut* through lumbar puncture. The means that have proved best are rest in bed, diet poor in meats, protracted warm baths, and roborants. The phosphorus liver oil had been especially recommended in cases complicated with osteomalacia. In the tetany of sucklings, *Escherich* recommends the interpolation of days with just adequate diet; it is especially important to substitute natural feeding for cow's milk whenever possible. Worthy of notice is the statement of *MacCarrison* that some cases of tetany disappeared when the patient moved to another place. In women conception should be prevented or even pregnancy interrupted. Certain drugs, such as ergotin, are to be avoided in the tetany of pregnancy (*Novak*).

*Gastric tetany* deserves an especial consideration. Here the question of operation (gastroenterostomy) has met with lively discussion. While *Albu* recommends operation as soon as possible, *Fleiner* would first await the results of internal therapy. Also *Chvostek* favors internal treatment. The results of the surgical treatment now seem very much to encourage this method of treatment. According to the latest statistics by *Wirth*, of twenty-one operated cases, seventeen remained permanently cured, while according to an older statistics of *Albu* the mortality of cases treated internally reached 77 per cent. The question is, however, rather more complicated than one would gather from these statistics. In case of certain pyloric stenosis, operation is indeed not to be rejected, the question is only whether operation should be undertaken immediately or whether it should be postponed until we find that we can accomplish no good by attempts to improve through internal treatment. Much will depend upon whether gastric lavage can be borne. Much difficulty is met with, however, in the diagnosis of pyloric stenosis. Cases of *Reichmann's* disease may present all the symptoms of pyloric stenosis—increased peristalsis in front of a Röntgen screen, indeed even antiperistalsis. Even in cases of true gastric tetany we saw not only a disappearance of the tetanic symptoms but also a lessening of the size of the stomach and a cessation of the spasm of the pylorus—this as the result of gastric lavage during the entire evening, and the administration of a dry diet rich in fats and of enemas to satisfy thirst. In such cases perhaps operation would be without curative results.

### (b) Conditions of Hyperfunction of the Parathyroids

Certain cases of adenoma of the parathyroids are known, without there having been found conditions that would be regarded as those of hyperfunction (*Erdheim*). Also the tumors, in size up to that of a child's head, described by *Benjamin*, *Hulst*, and *de Santi*, were attended with symptoms that were purely local, and otherwise remained without symptoms. In paralysis agitans, which was brought into relation with the parathyroids by *Roussy* and *Clunet*, *Erdheim* found the parathyroids normal in three cases and *Lundborg* and *Chvostek* ascribed myasthenia pseudoparalytica to hyperfunction of the parathyroids. *Chvostek* sought to establish that the clinical pictures of myasthenia and tetany were diametrically opposed to each other. Both would seem to affect the voluntary muscles with noninvolvement of the sphincters. The electrical behavior in myasthenia is directly opposite to that in tetany, and in the one is found fatigue of accommodation, in the other accommodation spasm. Each sometimes accompanies myxedema or Basedow's disease. The finding of the collection of cellular infiltrations and of discontinuous fatty degeneration of the muscle fibers, that is extraordinarily frequent (for literature see *Marburg*), points rather to the fact that myasthenia belongs more to the diseases of the muscular system; moreover, *Haberfeld* recently has been unable to find any alteration of the parathyroids in the cases of myasthenia gravis (see also the first chapter).

## Addendum

The author's criticism that some of the negative results of thyroparathyroidectomy may be due to the leaving behind of inaccessible parathyroids or portions of parathyroids seems also to the opinion of *MacCallum*, *Thomson*, and *Murphy*. At all events it appears that adult herbivorous animals (the sheep, *Simpson*) are capable of sustaining thyroparathyroidectomy without appreciable effect, although in *Simpson's* experiments the lambs that were operated on developed acute tetany and died.

The results obtained by *Mustard* on transection of the spinal cord agree with *Biedl's* and *MacCallum's* in that they are diametrically opposed to *Munk's* and to *Falta's* as to noncontinuance of tonic contractions in the parts below the seat of cutting after transection of the spinal cord. It is a pity that the divergence in results—whether they are due to interpretation or differences in technique—have not as yet been explained.

*Hoskins* and *Wheeler* have tested the effects of the injection of nicotin, adrenalin, and pituitrin in parathyroidectomized dogs, and have found that in these dogs there is a marked increase of vasomotor irritability affecting all components of the vasomotor mechanism, sympathetic cells, myoneural junctions and musculature.

*Underhill* and *Blatherweck* show that during the tetany which develops after thyroparathyroidectomy, glycogen disappears entirely from the liver and the sugar content of the blood is markedly lowered or may even be reduced to zero. It is probable that this action may be ascribed to the lack of parathyroid tissue, since the phenomena may be observed when all the parathyroids are removed and some thyroid tissue remains.

*Poll* and *Turnure* have transplanted a parathyroid into the preperitoneal tissue behind the sheath of the rectus muscle, in a case of tetany due to supposed operative removal of the parathyroids, with apparently good results, including cessation of the tetany.

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## CHAPTER V

## THE DISEASES OF THE THYMUS GLAND

It has not been long that the thymus gland has been classed with the hormonopoietic system. Originally it was regarded as a constituent of the lymphatic apparatus.

**Anatomy and Embryology.**—The thymus gland develops as a paired organ from the ventral part of the third branchial cleft. (See illustration 3, p. 53.) Both pairs unite very early; at birth the organ lies behind the sternum, backward as far as the pericardium, reaching above somewhat higher than the jugular notch. In the human being there may indeed occur accessory lobes of the thymus that may be either independent or united with the thyroid gland, or even the thymus gland itself. The thymus gland is therefore of entodermal origin; although at present there is no unity of opinion with regard to the origin of the pictures resembling lymphocytes found in the completed thymus and especially in its cortex. Since the investigations of *Hammar* the entodermal origin of the polymorphic fixed reticular elements lying chiefly in the medulla, and of the so-called *Hassal's* corpuscles stands assured. *Stöhr* regards the origin of the thymus lymphocytes as due to a partition of the epithelial pictures, while recently *Hammar* and *Maximow*, following the older assumption of *His* and *Stieda*, adhere to the assumption of a secondary ingrowth of mesodermal pictures. According to the latter view the thymus gland therefore belongs to the lymphatic apparatus; there is found in it a "symbiosis of cells of the different germinal layers;" it is concerned with the production of lymphocytes. According to *Nägele* it is indeed the principal site in the formation of the lymphocytes in early life. According to *Nägele* this view is also favored by phylogenetic factors, for in the amphibians the thymus is the source of lymphocytes when the lymph glands are still absent. The statement of *Ivar Bang* that the thymus gland contains at least five or six times more nucleinate than the lymphatic glands does not speak unconditionally against this assumption, as the analysis included the epithelial elements.

The weight of the thymus gland increases after birth, according to the statement of *Hammar, v. Sury, Schridde, Ronconi, Pappenheimer* and *others*, the growth ceasing only with the beginning of sexual maturity; the thymus tissue gradually atrophies and is partly replaced by fat, although appreciable remnants of thymus tissue are retained until late life. In late life too were found, by *Hammar*, mitotic proliferation of lymphocytes and new formation of *Hassal's* corpuscles. In addition to this involution of age occurs also an accidental involution; *Hammar* and *Jonson* have shown that in fasting animals the weight of the thymus gland reduces very rapidly, especially through loss of lymphocytes. Also in the melting down of the thymus gland on irradiation with X-rays, the reticulum shows itself much more resistant than the lymphocytes. The accidental involution is found among chronic diseases that lead to marasmus. It is especially well expressed in pedatrophy (*Farret*). Also, according to *Hammar*, accidental involution may occur in older people, an evidence that glandular tissue capable of functionating has still been present.

**Physiology.**—Concerning the question as to whether the thymus gland is an organ important for the life of the organism has not until recent times received a uniform answer. *Friedleben*, *Langerhans* and *others* saw animals in whom the thymus gland had been removed go undisturbed in their development, while other authors on the contrary, of whom I here mention only *Tarulli* and *LoMonaco*, *Ghika*, *Cozzolino*, *Basch*, *Sommer* and *Flörken; Ranzi* and *Tandler* saw occur in dogs, rabbits, cats, and other animals, temporary serious disturbances of growth which later disappeared. The most recent investigations are those of *Klose* and *Vogt* and of *Matti*. The investigations make it very likely that the disturbances mentioned can no longer disappear when the extirpation of the thymus gland has been done on very young animals only a few days old.

*Klose* and *Vogt* operated on twenty-five dogs. The phenomena observed are briefly as follows: After the latent stage of about fourteen days the animals gradually showed a spongy, soft skin, a "pasty habitus." They began to remain behind in growth on account of a lessened growth in length of the extremities. The bones were greatly and distinctly more flexible. In agreement with *Basch*, *Klose* and *Vogt* found that the ossification is retarded and that if the bones are fractured callus formation is very poor or does not occur at all. The ash contents of the bones is essentially diminished. *Basch* also found that in this stage the elimination of calcium is essentially increased.

The hyperexcitability to galvanism which *Basch* found in thymectomized animals is to be referred to the associated extirpation of the parathyroid bodies imbedded in the thymus tissue.

According to *Ranzi* and *Tandler*, the dentition is also delayed in this stage; the dogs take on abundant fat (stadium adipositatis, according to *Klose* and *Vogt*). This is followed by a stadium cachecticum; in spite of increased hunger the animals gradually lose weight, muscular tremors occur, the hemoglobin contents and erythrocyte contents of the blood reduce, and chemotactic irritants, such for examples, injection of nucleinic acid, remain inactive. The animals become indolent and tired, begin to suffer with disturbances of coordination and finally die in a coma-like condition. Feeding with thymus gland or injection of it only aggravates the condition.

*H. Matti* describes the condition after thymectomy in very young animals as somewhat different. After the latent period of about four weeks, during which the animals remain behind in growth, manifestations occur in the osseous system that are very much like those of high-grade rachitis. There occur a high-grade softening and bowing of the bones and a rosary formation; there is found a deficient apposition of calcium in the bones, the bone marrow is hyperemic and the metaplasia in the fat marrow is slowed. The epiphysial junctures are several times broadened. The examination of the blood only shows that the decrease in lymphocytes that normally occurs with increasing age and the increase in neutrophilic elements is slowed. *Matti* found the suprarenal marrow broadened, in addition to which was found a slight enlargement of the thyroid gland and of the pancreas. The gray substance of the spinal cord shows, as *Klose* and *Vogt* have already stated, signs of an increased breaking up. At the close the animals lose the ability to walk and there ensues marked cachexia that leads to death. The muscles show high-grade atrophy of inactivity, with transitions to degenerative atrophy.

In thymectomy in somewhat older animals these manifestations occur only temporarily, yet when the extirpation was associated with removal of the spleen, the animals, according to *Klose* and *Vogt*, for the most part died. This would signify that the spleen takes over at least a part of the function of the thymus gland. *Matti* could not find this.

It should be mentioned further that castration in young animals essentially delays the involution of the thymus gland and that increased sexual activity accelerates it (*Calzolari*, *Henderson*, *N. Paton*, and *Goddall*, and *others*). With this agrees the fact that in eunuchs, *Tandler* and *Gross* found the thymus gland to be hyperplastic.

*Svehla's* experiments on hyperthymization have in part lost their significance, as it has been shown by *Popper* that the depressor action of thymus extracts intravenously is not specific, but is dependent on clots in the blood path.

**Pathology and Semiology.**—Our knowledge as to the *significance of the thymus gland in clinical medicine* is extremely deficient. As far as symptoms in the *absence of the thyroid gland* in human beings is concerned we know next to nothing.

In the autopsy of new born and very small children *aplasia* of the thymus gland has sometimes been found. The first statement is that of *Bischoff*. *Clark* described an eight-months-old child that was well up to the sixth month. Then there developed hydropic swellings. Autopsy showed left-sided hydronephrosis and aplasia of the thyroid gland. *v. Sury* describes a case of congenital total defect of the thymus gland in a three-month-old child who died of pneumonia. Aplasia of the thymus gland seems very frequently to be associated with other malformations and especially in developmental defects of the brain (*Winslow*, *Borneville*, *Katz*, and *others*). On the other hand, *G.*

*Anton* shows the simultaneous occurrence of thymus hyperplasia and brain hypertrophy.

Lately total extirpation of the thymus gland has been carried out on account of stenosis of the trachea (see below). Very worthy of note is the statement of *Koenig*, that after resection of the thymus gland such as was undertaken in a nine-months-old child on account of dyspnea, breathing became normal and afterwards there developed a severe rachitis on account of which the child first learned to walk as late as the age of four and one-half years. In the rest of the cases there are no statements as to the further course. According to the experiences in animals, the experiments up to the present, total extirpation of the thymus gland in very young children is to be advised against.

Up to the present the entire clinical interest has been turned to the cases which have shown a *hyperplasia* of the thymus gland and a *persistence* or reviviscence of the same.[1] *Kopp* in 1855 first attracted the interest of the medical world to the cases of sudden death in early life which occurred with cyanosis and stridor and which on section showed nothing but hyperplastic thymus gland. The extensive investigations of *Friedleben*, which culminated in the aphorism "there exists no thymic asthma," for a long time suppressed this teaching. First in the year 1888 *Grawitz* on the evidence of two cases pointed out the forensic significance of thymic hyperplasia. Up to this time only purely mechanical factors in these cases of death had been considered. Then in 1889 *A. Paltauf* finding out the frequent combination of thymic hyperplasia, status lymphaticus, and narrowing of the vascular system regarded the cause of death not as a mechanical factor but as a vegetative disturbance which he designated as lymphato-chlorotic constitution. Among others, *Ortner* reported congenital narrowing of the aortic system in these cases of sudden death, *v. Kundrat* status lymphaticus with more or less large thymus gland in cases of sudden death in narcosis, *Schnitzler* and others narcotic death in cases of Basedow's disease with persistence of the thymus and status lymphaticus. With *Pott* originated an excellent description of the cases of sudden death in the years of childhood. The most authors agree with the view of *A. Paltauf*, in that they regard the mechanical factor as without significance and place in the foreground the lability of the organism or the cardio-vascular system which is dependent on toxic factors. Especially interesting are the observations of the familial occurrence of these species of sudden death (*Perrin, Hedinger*, and *others*). Certain authors, however, hold fast to the mechanical cause through compression of the trachea by the thymus gland.

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[1] Persistence of the thymus gland is, properly speaking, an incorrect expression as every human being possesses a thymus gland for his whole life time. Better than "persistence" is higher parenchymal value than corresponds to the age; also a reviviscence is really not certain, as we do not possess a criterion for it.

The question is not completely cleared up at the present day although the direction in which we may expect the clearing is indicated. What makes the question especially difficult is the circumstance that status lymphaticus and enlarged thymus gland occur so frequently in associationship. Apparently, however, they stand to each other in a conditioned relation. As we shall see later in another paragraph, the finding of an intumescence of the lymphatic apparatus eventually with a mononucleosis in the blood is very frequent indeed. We find these in numerous diseases of the ductless glands, in chronic infectious diseases, in neurosis of the vagus nerve, etc. These hyperplasias deviate markedly from one another histologically. In addition, it is perfectly clear that not every chronic swelling of the lymphatic apparatus is associated with increased chemic function. Also the thymic hyperplasia or thymic persistence or reviviscence is extraordinarily frequent just in these diseases of the ductless glands. If we allow ourselves to accept the view that the thymus gland is in part of mesodermal origin, therefore in part belongs to the lymphatic apparatus, this frequent combination of enlarged thymus gland and status lymphaticus would not be inexplicable. There certainly exists, however, an abnormally large thymus gland without status lymphaticus, hence a status thymicus.

Recent investigations seem to have furnished a significant differentiating criterion. *Wiesel* and *Hedinger* have shown that status lymphaticus is associated with a hyperplasia of the chromaffin tissue. Thus *Hedinger* found in five cases of pure thymic hyperplasia entirely normal development of the suprarenals and the entire chromaffin tissue, also on microscopical examination. Also *v. Sury* points out that in the so-called thymic death of the new-born the chromaffin tissue is always well developed and that the hypoplasia of the chromaffin tissue sets in only with the development of status lymphaticus. In cases of pure thymus hyperplasia the lymphocytosis of the blood would seem to be absent.[1]

Let us now turn again to the question of *thymic death*. *v. Sury* has treated this subject in an elucidative exposition, one especially adequate on account of its rigid critique. He bases his conclusions on the material of two hundred medicolegal autopsies in which the thymus gland was taken into account. *v. Sury* shows first that the thymus gland varies extraordinarily in size and that therefore the diagnosis of a thymus hyperplasia is often very arbitrary. He mentions further that in the cases of sudden death in children apparently healthy beforehand there exists very frequently capillary bronchitides that are very common and that are very easily overlooked. In spite of this we can hardly deny the significance of the mechanical factor in the cases of "*thymic asthma*" published in recent years. Cases which after partial or complete extirpation of the thymus gland became greatly relieved of their oppressive symptoms. *Klose* and *Vogt* have collected eight such cases. The first case was operated on by *Rehn* (reported by *Parucker*). It was that of a two and a half year old child. Since that time a series of other cases have been operated on (see the literature in *Wiesel*). Especially to be mentioned is the case of *Hinrichs* in which the hyperplastic thymus gland in addition to a hindrance of breathing led to a high-grade disturbance of the ingestion of food. Lately the action of the X-rays has also been recommended (*Friedländer, Myers, Rachford, Ribideau* and *Weil*). The case of *Ribideau* was that of a two-month-old child with marked need for air on account of hyperplasia of the thymus. After extensive irradiation with X-rays the dyspneic manifestations disappeared within two days; somewhat later death occurred on account of measles. The autopsy showed fibrous atrophy of the thymus gland.

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[1] Often in pure status thymicus the epithelial thymic tissue, that is, the reticulum and its derivatives, is found hyperplastic while the small thymic cells do not necessarily have to be increased, in contrast with status lymphaticus (*Wiesel*).

The attacks of dyspnea, cyanosis, stridor, and eventually hoarseness, that were observed in all these cases speak indeed for a purely mechanical factor. Whether in the pure cases of status thymicus in addition to this mechanical factor there exists a toxic factor on account of hyperthymization we must for the present leave undecided; although I have hardly been able to discover any grounds for this assumption. Up to the present the cases of Basedow's disease known in which death occurred suddenly in narcosis regularly showed in addition to thymus hyperplasia a pronounced status lymphaticus and were in addition complicated by other factors.

It should be mentioned further that the thymus gland can also be the seat of *malignant tumors* or of inflammatory processes. The numerous thymic tumors thus far observed have not furnished any information as to the physiology of the gland. *v. Neusser* described a case of sarcoma of the thymus gland. A twenty-five-year-old patient was remarkably large and showed hyperplasia of the genitalia. A short time ago we observed a case of carcinoma. Here also there existed gigantism. The development of the genitalia was, however, entirely normal. There should also be mentioned the case of *Bramwell* in which was found, in addition to the sarcoma of the suprarenal gland, a carcinoma of the thymus. Finally in numerous, but not all, cases of myasthenia gravis there were found hyperplasia of the thymus gland and alterations in the muscles that were regarded as lymphosarcoma. This interpretation is not however certain, as *Hassal's* corpuscles occur in the muscle metastases. In these cases we are dealing rather with reticulum tumors.

If when we try to draw a resumé out of the facts detailed we find that it cannot be denied that in spite of the enormous labor that up to the present has been spent on this subject, the physiological significance of the thymus gland is still unclear. The destruction of the organ through tumors or inflammatory processes which have otherwise furnished us with so much important information in the pathology of the other ductless gland is here apparently entirely without significance. Operative extirpations of the gland in earliest childhood have, except in the single case of *König* previously mentioned, furnished no symptoms of absence. However, we should not forget that we mostly deal with cases of resections and that also in most of the cases statements as to the further course were absent. Then again we must consider the presence in such cases of accessory lobules of the thymus.

Just as little clarified appears to me the significance of thymic hyperplasia for pathology. In many cases only the significance of the mechanical factors remain certain; this is however quite without significance for the question of hyperthymization. For the rest we really only know that in a great number of very diverse conditions we find thymus glands with supernormal parenchymal values. Especially is this true for diseases of the ductless glands. We find thymus hyperplasia very frequently in Basedow's disease, apparently also in acromegaly, in hypophysial dystrophy, in myxedema, in eunuchoidism, etc. *It therefore occurs as well in conditions of glandular hyperfunction as in hypofunction.* I believe, therefore, that we should exercise great scepticism concerning theories that especially would explain the frequent coincidence of Basedow's disease and thymic hyperplasia. On the same ground I regard as at present quite hypothetical the correlations that according to the views of many modern authors exist between the thymus gland and the other glands of internal secretion.

Also the experiments to produce hyperthymization artificially have up to the present seemed scarcely satisfactory. The old experiments of *Svehla* are, as has already been mentioned, not of value as evidence. The fewer experiments of *Hart* with injection of powdered Basedow's thymus and those of *Bircher* with implantation of Basedow's thymus in animals are worthy of notice but do not furnish sufficient grounds for the support of a teaching of hyperthymization.[1] Also the hypothesis that *Wiesel* provides at the end of his uncommonly well prepared work on the pathology of the thymus seems to me on the face of it as still too little supported. *Wiesel* supposes that the thymus gland furnishes to the blood path a secretion that acts vagotonically, and he regards especially the eosinophilic cells present so abundantly in the thymus gland as the seat of origin of this principle that acts antagonistically to adrenalin. In this respect then *Wiesel* identifies status thymicus and status lymphaticus, although he does take pains to separate the two conditions from each other in an anatomical sense.

## Addendum

*Boggs* points out, without regards to the dulness due to enlarged thymus is partially higher and more superficial than that due to diseased mediastinal lymph glands or other forms of mediastinitis; that it is constantly much more marked on the left of the sternum than the right, and the dulness is movable, the lower border rising as much as an interspace when the head is shifted from extreme flexion to extreme extension, with the patient in the sitting position. "In some cases of persistent or enlarged thymus there may be no dulness in the first interspace, but only in the second and below it. In such instances a shift in both upper and lower borders of dulness may be made out."

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[1] Concerning the "thyrogenous" Basedow's disease see chapter on thyroid gland, pp. 75 and 90.

The movement in the dulness of the thymus is explained by the author as due to the movability of the thymus itself. He found the thymus to be enlarged or persistent in thirty-five of sixty-six colored girls, between the ages of five and eighteen years, fourteen of whom had suffered from measles. He remarks that lymphatic hyperplasia seems more common in the colored race. *Jacobi*, in the discussion on *Bogg's* article, recommends percussing with the child in the prone position.

*Park* and *McGuire*, however, on the basis of twenty-nine autopsies, have determined that the thymus gland is a relatively immobile organ and that the methods of percussion used by *Jacobi* and by *Boggs* bring out a movable dulness that is due to other factors, probably to the upward advance of the lung margins.

Of recent cases of apparent thymic death, it is probable that death in the cases of *Ginsburg* and of *Kennedy* was due to mechanical factors, while in *Veeder's* case, it is not at all certain that the thymus had anything to do in the matter.

In a recent review, *Ricketts* mentions the various surgical procedures on the thymus gland, and points out that in case of impending suffocation due to enlarged thymus, intubation or tracheotomy may be done.

According to *Halsted*, *Klose* warns against X-ray irradiation of the thymus region in young children, because of the marked susceptibility of the gland to the influence of the X-ray.

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## CHAPTER VI

## THE DISEASES OF THE HYPOPHYSIS [PITUITARY GLAND]

Since *Pierre Marie* delineated the clinical picture of acromegaly and placed it in an etiological relationship to the hypophysis, the literature on the experimental research and clinical study of the hypophysis has grown enormously. In spite of this fact there as yet prevails in our views as to the pathogenesis of the clinical pictures concerned with the hypophysis very little uniformity. The chiefest cause of this is that as yet we know but little as to this organ's physiological significance, at least much less than we know about the thyroid. For this is to blame principally the difficult accessibility of the gland for experimental purposes, and further the fact that here we have to do with two organs intimately bound together and enclosed in a rigid bony cavity. A certain physiological independence of these two organs might be expected from their morphological and embryological independence. Hence we may speak of a hypophysial apparatus showing certain analogies with the thyroid apparatus (thyroid gland and parathyroid glands) and with the corresponding suprarenal apparatus (cortex and chromaffin medulla) hereafter to be described. The differentiation of the pathological manifestations occurring to the two systems is made more difficult than that of the pathological manifestations affecting the other ductless gland groups because on account of the enclosure in a rigid cavity an affection of one of the organs seldom leaves entirely uninvolved the other.

In an attempt to delimit and to explain the clinical pictures presented by the hypophysial apparatus the following four points seem to begin to be important. 1. The characteristic typographical relations, 2. the embryological development, 3. a certain physiological independence, and 4. the manifold analogies that exist between the glandular organ of the hypophysial apparatus and the thyroid gland.

**Anatomy and Embryology.**—The normal hypophysis of man weighs on the average somewhat more than 0.5 gm. It consists in a glandular anterior lobe and a nervous posterior lobe. Both lie in the sella turcica, into which cavity the dura penetrated through the foramen sellæ turcicæ and surrounds them both in common. From the anterior lobe a small process projects forward in the so-called peduncle of the hypophysis while the posterior lobe is directly in communication with the brain by means of the infundibulum. A tapering cleft, the recessus infundibuli, in communication with the third ventricle, penetrates deeply into the peduncle.

The following scheme after *Erdheim* shows these relations: *Ch.* =

chiasm; *V.L.* = anterior lobe; *H.L.* = posterior lobe; *Pl.eh.* = accumulations of squamous epithelium; *R.C.* = *Rathke's* cysts; *F.* = process; *E.* = terminal enlargement of process; *r.i.* = recessus infundibuli; *I.* = infundibulum; *D.* = dura; $D_2$ = diaphragma sellæ; *A.* = arachnoid.

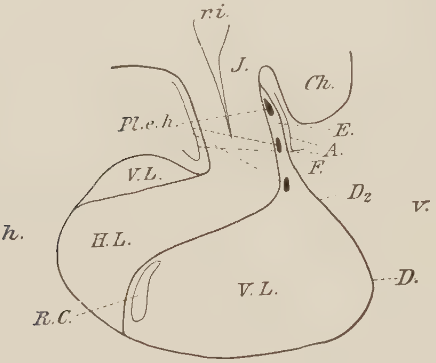

FIG. 30.—Diagram of the structure of the hypophysis (after *Erdheim*).

The anterior lobe is supplied by small branches of the internal carotid artery, the posterior lobe by vessels of the pia. The veins end in the sinus circulosus Ridleyi. Anterior and posterior lobes are surrounded by a capsule of the dura mater, which capsule overhangs the entrance to the sellæ in the form of a diaphragm that is perforated by the infundibular peduncle.

The anterior lobe for the most part consists in epithelial columns. Here are found chromophilic cells in which *Benda* by the employment of a specific stain has demonstrated eosinophilic and basophilic granules. Here are also

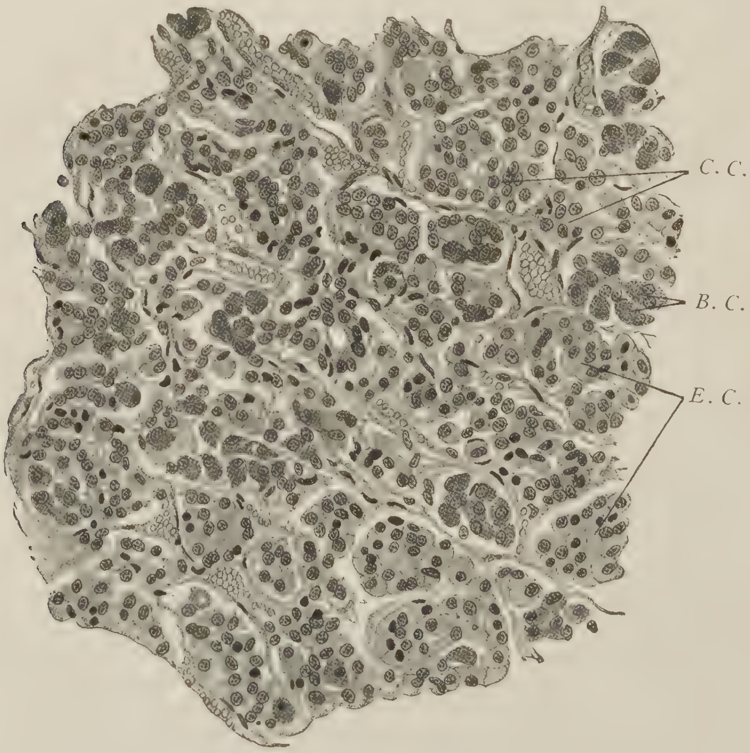

FIG. 31.—Anterior lobe of the hypophysis. *E.C.* = eosinophile cells, *B.C.* = basophile cells. *C.C.* = chief cells.

found cells that are nongranular; the so-called principal cells, which during pregnancy, according to *Erdheim* and *Stumme*, develop into the so-called pregnancy cells.

Posteriorly the anterior lobe is delimited from the so-called pars intermedia by a poorly vascularized layer of connective tissue. The especial histological character of the pars intermedia has been made prominent especially by *Herring*. Here are found follicle-like pictures filled with colloid. This cellular layer has also been called the cork layer or *Peremeschko's* medullary layer. There lies also the so-called *Rathke's* cyst.

The posterior lobe is made up of glial tissue and scattered cells, the character of which has not as yet been established, and of nerve fibers.

The hypophysis of man undergoes characteristic alterations during pregnancy. First *Comte*, in six pregnant women, found enlargement of the hypophysis and multiplication of all the sorts of cells. Later *Erdheim* and *Stumme* made a careful study of the alterations. According to both these authors the enlargements affect only the anterior lobe. The differences in size are very appreciable. While the weight of the hypophysis in a nullipara is about 61.8 cgm. on the average, *Erdheim* and *Stumme* found it to be on the average 84.7 cgm. in primiparæ and 106 cgm. in multiparæ.

Through its position the hypophysis shows special relations to the chiasm of the optic nerves and to the third and sixth cranial nerves.

The *embryological* development of the hypophysial apparatus is shown in the following three sketches, which are taken from the works of *Erdheim* and of *Mihalkovic*.

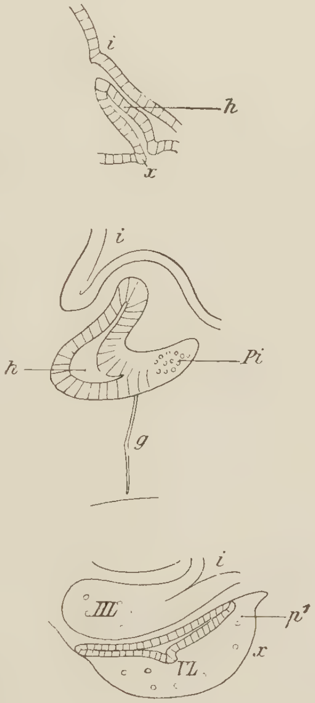

FIG. 32.—Development of the hypophysis.

$i$ = infundibulum.
$h$ = Rathke's pouch.
$x$ = boundary between epithelium originating from the primary ectodermal oral diverticulum, and the entodermal head-gut.
$Pi$ = solid process (anterior lobe).
$g$ = hypophysial duct.
$x$ = original insertion of the hypophysial duct.
$p_1$ = process of the grown-out [ausgewachsen] normal hypophysis.
$x$ = collection of accumulations of squamous epithelium, probably remnants of the hypophysial duct originating from the epi-

thelium of the oral diverticulum, while the epithelium of the hypophysial duct is cubical.

The nervous lobe of the hypophysis originates from the diencephalon. Here there develops a pouch-like protrusion processus infundibularis), which during the fourth week adjoins a similar pouch originating from the epithelium of the oral diverticulum (*Rathke's* hypophysial pouch). In the lower classes of animals there exists an intimate spatial relationship between the two, due to the fact that the infundibular peduncle, which in these animals is much better developed, is overlain in a cup-like manner by the epithelial part (see *Edinger*, Bau der nervösen Zentralorgane des Menschen und der Tiere, 2, Bd. 7 Edition, 1908). In man this intimate relationship between anterior and posterior lobes is by no means so extensive. Here principally the posterior lobe is very much less well developed.

The question as to whether the pars intermedia belongs to the anterior or to the posterior lobe seems to me, according to what I can find in the literature as to this subject, as yet not cleared up. At all events the facts are important that on separation of the anterior lobe from the posterior the pars intermedia always remains with the posterior—a fact also mentioned by *Cushing*—and that, as had already been mentioned, the anterior lobe and the pars intermedia are always separated by a layer of connective tissue. This question seems to me to be a very important one from the clinical standpoint. As is known, the posterior lobe and the pars intermedia contain a substance that increases blood-pressure and acts as a diuretic, a substance that in its action shows a certain similarity to adrenalin. It is, therefore, not impossible that the pars intermedia possesses in its relation to the nervous system similar embryological relations to those which have been demonstrated for the chromaffin tissue.

The analogy in the development of the glandular lobe of the hypophysis with that of the development of the thyroid is apparent. Both originally are glands with external secretion. Just as is the case with the hypophysial duct, the ductus thyreoglossus undergoes atrophy; this also leaves behind cell accumulations which consist chiefly of stratified plaster epithelium. According to the recent investigations of *Haberfeld* the hypophysial duct may, especially when there are malformations of the skull, persist. This has also been observed in acromegaly (*Ettore Levi*). It is of especial significance for the pathogenesis of acromegaly, as we shall see later that accumulations of typical glandular epithelium may be found on the roof of the pharynx as well as along the persistent craniopharyngeal canal, from which accumulations may be formed adenomata.

The glandular anterior lobe of the hypophysis is a true ductless gland. The opinion has been expressed that its secretion streams off through the posterior lobe. Against this speaks first the separate blood supplies, then the fact that the posterior lobe may be removed without the anterior lobe's losing its function (*Crowe, Cushing* and *Homans*), and finally the observation of *v. Cyon* that in hypophyses of cattle and sheep the anterior and posterior lobes may be separated from each other by small plates of bone. It may well be supposed that as is true for the external secretion of thyroid, the exit channel for the internal secretion of the anterior lobe is formed by the lymph-vessels or the blood-vessels.

The secretion of the posterior lobe would seem to pour out into the third ventricle through the recessus infundibuli. *Cushing* and *Götsch* in animal experiments found that the cerebrospinal fluid increases the blood-pressure in a manner analogous to the action of infundibular extract. I would like to see demonstrated the fact that the cerebrospinal fluid acts as a diuretic as does pituitrinum infundibulare.

## a. Acromegaly

### Hyperpituitarism, Marie's Disease

**Definition.**—*By acromegaly we understand a disease that is characterized by the gradual enlargement of the peaked [gipfelnde, i.e., peaked, acral] parts (nose, lips, tongue, lower jaw, hands and feet) and by hyperplastic alterations in the entire osseous system. There mostly develops an appreciable enlargement of the hypophysis, which leads to broadening of the sella turcica. Associated with this is localization of corresponding symptoms of brain pressure. To this should be added very frequently alterations of the thyroid gland of a hyperplastic character, marked accentuation of the function of the interstitial glands, also very frequently loss of function of the genital glands after preliminary transitory increase of function, and, apparently frequently, hyperplasia of the suprarenal cortex. Also the condition of excitability of the vegetative nerves is sometimes increased in manifold ways. Very frequently occurs rapid withering away of the body and manifestations of degeneration of manifold nature. The pathological anatomical finding in the hypophysis is an adenoma or adenocarcinoma of the anterior lobe. To-day we refer acromegaly to an increase of function of the glandular hypophysis.*

**Occurrence.**—Acromegaly is no very rare disease. It does not seem to give preference to any country or to any race of people. It usually begins between the ages of twenty and forty years, most frequently between the twentieth and thirtieth year of life (*Sternberg*). According to this author it usually occurs in women later than in men. There are also rare cases of acromegaly that begin in the years of childhood or adolescence. These are of special importance. I shall refer to them in greater detail in the consideration of the pathogenesis. Hereditary or familial occurrence seems to be very rare. I have found very few statements as to this question in the literature and all these are very indefinite. Thus *Arnold* in

1891 described in detail a case of acromegaly that began in the eighteenth year of life. One of the patient's brothers was affected with the same disease earlier in life. Also *Fräntzel* describes a case in which the affection began in boyhood; in the eleven-year-old daughter of which patient the disease was also recognizable. Very many large people were members of this family. We find a statement of *Schwoner's* that the mother of the female patient who was seventy-three years old apparently became sick with acromegaly at the age of fifty; the father of the patient was also very large. *Fränkel*, *Stadelmann* and *Benda* state that the father of two blood relations of the case described by them was said to have shown the same anomaly. In the case reported by *H. Salomon*, we find the statement that the mother of the patient seems to have suffered with acromegaly and diabetes.

**Symptomatology.**—I begin with a description of the alterations in the *bones and soft parts.* The alteration of the face in fully developed cases can be so marked that the individuals actually become unrecognizable. The nose is monstrously thickened, the superciliary arches and malar bones protrude markedly; this is chiefly dependent on an increase in volume of the pneumatic cavities. I refer to the X-ray illustration of Observation XXV in which the large frontal cavity is to be seen as a light space. Such an enlargement may bring about narrowing of the auditory passages and of the orbits. In the case of youthful acromegaly described by *Schultze* and *Fischer* there occurred almost complete deafness probably due to the thickening of the internal ear. Also the cranial skull may increase essentially in circumference so that the hats no longer fit. The sutures often close prematurely. The external occipital protuberance is in most cases enormously developed. The narrowing of the organs may bring about exophthalmus although this may be also brought about by other causes such as enlargements of the bulbs and stagnation in the cavernous sinuses (*Benda*). In many of the cases associated with symptoms of Basedow's disease the cause of an existing exophthalmus may be due also to a heightened tonus of *Müller-Landström's* muscle. The great variation that the exophthalmus shows in such cases may be as well explained in this manner as by the cause assigned by *Benda.*

Very characteristic is the spreading apart of the teeth on account of the enlargement of the upper jaw, especially of the lower jaw. On account of the marked prognathia of the lower jaw, and on account of the oblique position of the alveolar process due to this, chewing becomes almost impossible. The mucous membrane of the oral cavity is for the most part thickened, the tongue can so increase in size that in spite of the enlargement of the jaws it projects over the teeth. The mucous membrane of the tongue becomes thickened, the papillæ are enlarged, the microscopic examination showed enormous proliferation of the interstitial tissue, while the muscle fibers show, at least in the later stages, signs of atrophy and degeneration. On account of the thickening and the weight of the tongue articulation may be affected. The larynx is often considerably enlarged, the voice is deep and, on account of the resonance in the enlarged pneumatic spaces, abnormally loud. This is true for both male and female individuals. Quite especially are enlarged the clavicles. Often there develops rather quickly a pronounced kyphosis of the lower cervical and upper thoracic spine and a lordosis of the lumbar spine.

There may also occur ankylosis of the vertebral bodies. The ribs are thickened and broadened. Very characteristic is the tremendous thickening of the places for the insertion of the muscles, the widening of the vascular foramina and the deepening of the vascular furrows (*Sternberg*); the entire osseous system can be enlarged in all dimensions as in the cases of *Schultze* and *Fischer.*

On the hands only the soft parts are considerably thickened, the thickening occasioning a spreading apart of the metacarpal bones. The hands become paw-like. The X-ray picture does not show anything especially beyond a slight thickening of the places of muscular insertion (type en large, *Pierre Marie*), (see St, Observation XXX, reported later). In other cases there is in addition to this an increased growth in length, leading to a true giant hand (type en long see Ti, Observation XXV). Here are found both lengthening and broadening of the hands and feet. *Launois* and *Roy* find the type en long in acromegalic gigantism. The feet may behave similarly.

*X-ray examination* of the skeleton shows a thickening of the walls of the skull, enlargement of the pneumatic cavities, increase in size of the lower jaw and broadening of the epiphyses of the long bones, formation of osteophytes on these, thickening of the phalanges of the fingers and toes (*Schüller*); in the later stages of acromegaly there is found considerable atrophy of the osseous structure; on section *Deitrich* found especially the spongiosa atrophic. He regards this as neuropathic atrophy. *Fränkel*, *Stadelmann,* and *Benda* in each of four cases found pronounced atrophy, in one case distinct porosis and always formation of osteophytes.

As in the later stages the muscles of the arms and legs are for the most part markedly atrophic, the amorphic condition of the extremities becomes that much the more conspicuous.

As example of the skeletal alterations in acromegaly I cite the following case:

*Observation XXIV.*—V. U., thirty-two years old, entered the clinic Jan. 10, 1912, carpenter.. No hereditary predisposition to disease, no similar sickness in the family. Married seven years. One year after the marriage a child was born that died soon after birth. One illegitimate child is ten years old.

The present disease began seven years ago with a feeling of furriness in both hands, formications, and a characteristic sensation of stiffness especially in the morning. For some months *severe pains* in the hands and forearms so that the patient had to get up often at nights and walk about the room. Soon afterward the patient noticed *gradual enlargement* of the hands, and a short time after this the chin became larger so that *chewing was done only with the lateral teeth,* as also the jaw was pushed forward. The pains and paresthesias were always worse in summer than in winter. For five and one-half years gradual *loss of libido*, and later loss of *erectibility of the penis. Entirely impotent for five years.* The acromegalic alterations greatly increased in intensity. The patient denied headaches and disturbances of vision. Lately there have reappeared drawing pains, especially in the knees and ready fatigability; in addition to these, severe sweats. Alcoholism; patient denies lues.

Status.—168 cm. tall, coarsening of the facial features, cushioning of the lips, circumference of the skull 58 cm. Marked protrusion of the orbital borders and the frontal protuberances. Circumference of the skull from the point of the chin to the top of the occiput 74 cm. Nose coarse, large, lower jaw markedly protruding, lower *row of teeth is 1.5 cm. anterior to the upper row.* The lower incisor teeth gape 3 mm. Tongue markedly thickened and broadened and on account of the thick tongue, articulation is poor. Uvula broad, tonsils enlarged, neck broad and compressed 34½ cm. in circumference. Submaxillary glands palpable. *Thyroid enlarged*, left lobe more enlarged than right.

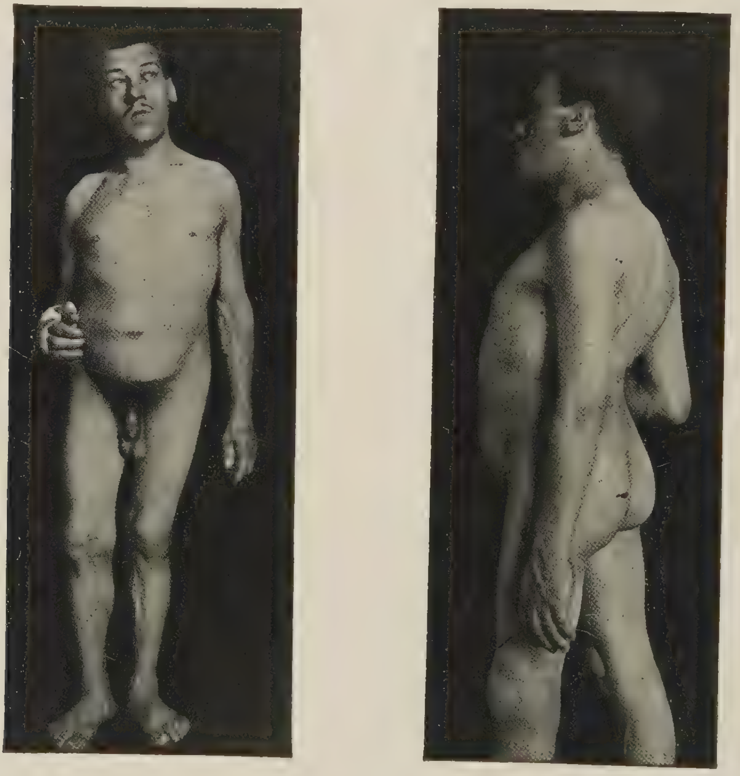

Fig. 33. Fig. 34.

Case of acromegaly (Observation XXIV).

The skin and visible mucous membranes somewhat pale. The skin rather thick but may be readily raised from the underlying tissues in great thick folds. The hair of the head rather abundant, the *hairiness of the genitalia rather marked* and also the thigh and legs are rather pronouncedly covered with hair.

Distinct *kyphosis* of the upper dorsal part of the vertebral column, slight lumbar *lordosis*. *Thorax is barrel shaped*, compressed, reaching deep downward in front. Circumference of the thorax at the level of the nipple is on deep inspiration 104 cm., on strong expiration 101 cm. *The clavicles are markedly thickened.* Also the ribs are strikingly broad, as are also the intercostal spaces. *The upper and lower extremities have taken on in circumference in their distal parts.* Abnormal breadth of the middle of the hand. Circumference of the middle finger 8½ cm. Right hand displaces 625 cm. of water, left hand 640 cc. of water. X-ray examination shows chiefly hypertrophy of the soft parts. The metacarpi are biscuit-shaped on account of the pressure of the increased soft parts and decrease in size at their diaphysial portions. Also the middle portion of the foot is enormously broadened, showing a similar picture to the X-ray. Enormous thickening of the toes.

*Transverse diameter of the heart to the X-ray 13 cm.* Otherwise cardiac findings normal. A slight decrease of tachycardia. Liver and spleen not palpable. On X-ray examination the stomach is not enlarged.

Examination of the eye. (Docent *Ulbrich*) O. D. 4/5, O. S. 5/10. External halves of the papillæ pale, with however a large physiological excavation so that the diagnosis paling is not possible. Visual fields for white and colors are normal.

*X-ray Examination of the Skull.—Enormous enlargement of the entire skull,* especially the facial bones. Sella turcica enlarged to the size of a gulden. *Clivus sharpened.*

Erythrocytes, about 4,500,000.

Hemoglobin, 75 per cent.

Leucocytes, 6,240 of which:

Polymorphonuclear neutrophiles, 57.6 per cent.

Lymphocytes, 25.4 per cent.

Large mononuclears, 15.7 per cent.

Eosinophiles, 1.3 per cent.

Examination as to alimentary glycosuria was unsuccessful, as the patient vomited. No sugar in the urine on the administration of a diet rich in carbohydrates.

Pulse between 90 and 100.

Examination of the exchange of gases (*Dr. Bernstein*).

| $CO_2$ | O | Respiratory quotient | $CO_2$ | $O_2$ |
|---|---|---|---|---|
| 235.7 | 288.8 | 0.816 | 3.156 | 3.857 |
| 240.7 | 296.3 | 0.793 | | |
| 243.2 | 298.4 | 0.781 | | |

The examination of the elimination of uric acid on a purin-free diet shows a marked increase of the endogenous factor. This lies higher than double the normal average (*Novaczinsky* and *Falta*).[1]

Examination of ammonia, amino-acids, and polypeptid elimination shows normal relations as may be seen by few figures here adduced.

| N | $N(NH_3)$ | N. ( amino acid) | N. polyp. |
|---|---|---|---|
| 16.64 gm. | 0.7202 | 0.2718 | 0.0683 |
| 18.65 gm. | 0.6902 | 0.2842 | 0.1561 |

On Feb. 28, a portion of the hypophysis of the patient was removed by the endonasal route by *Dr. Hirsch.*

Mar. 5, the patient was retransferred to the clinic.

Mar. 15, patient has fallen off in weight and the acromegalic symptoms have not as

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[1] On the administration of sodium nucleinate there was a prompt and rather high increase of the uric-acid elimination.

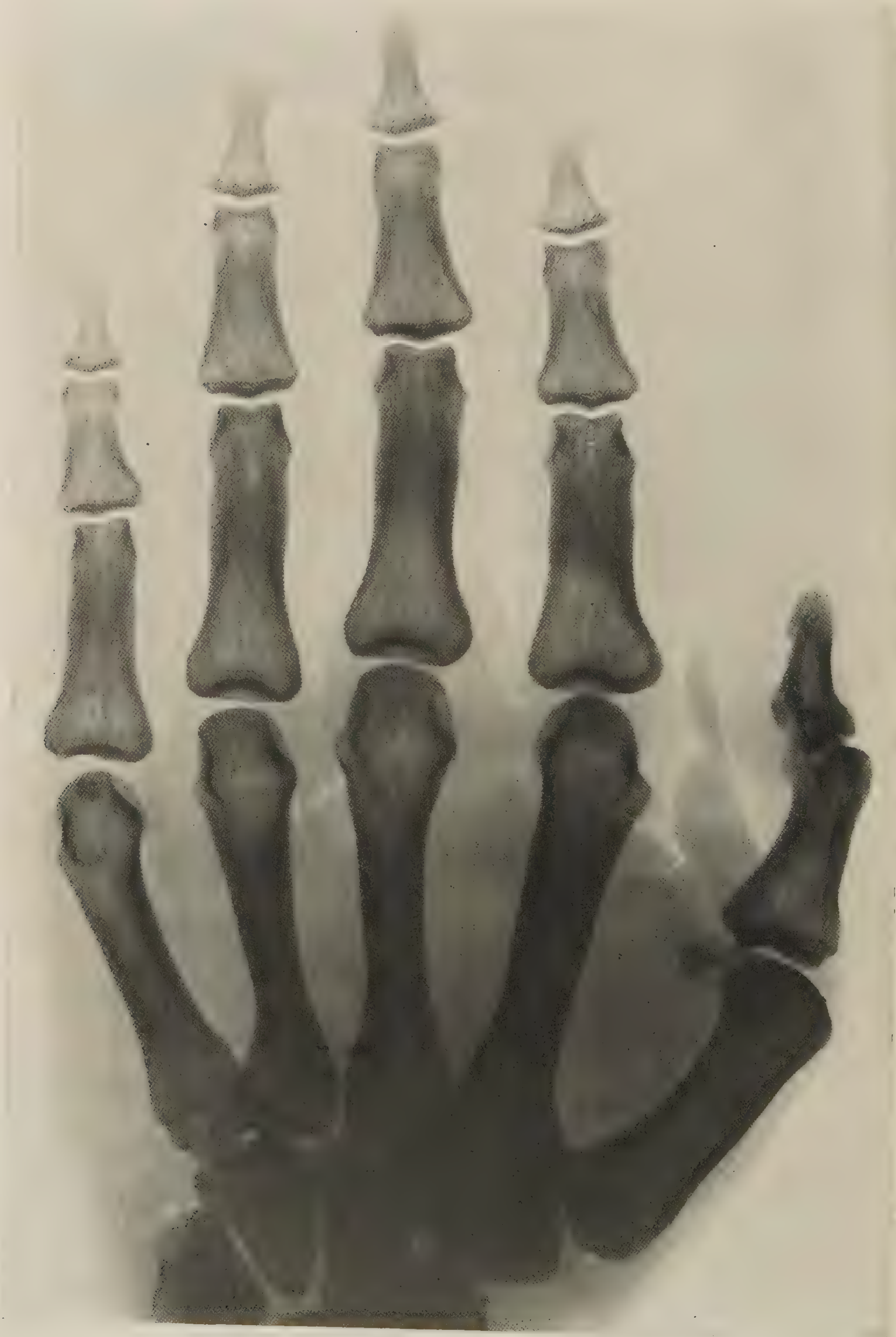

FIG. 35.—X-ray picture of hand in acromegaly (Observation XXV).

yet retrogressed. Several times at the beginning the patient showed a rise in temperature, but at present the temperature is normal. Headaches at times. Examination of the purin metabolism shows just as decided an increase of the endogenous elimination of uric acid as before the operation.

In many cases the *muscle strength* is not diminished in the initial stages. Sometimes such individuals show even an extraordinary strength. There is, however, from the beginning a gradually increasing and rapid fatigability, and in the later stages such individuals cannot long follow their occupation on account of muscular weakness. Microscopically such muscles show increase of the connective tissue and degeneration and atrophy of the muscle fibers. *Arnold* describes vacuolization, multiplication of the nuclei, and atrophy of the muscle fibers, increase in the number of nuclei, and growth of interstitial connective tissue, also the occurrence of fat cells in the connective tissues.

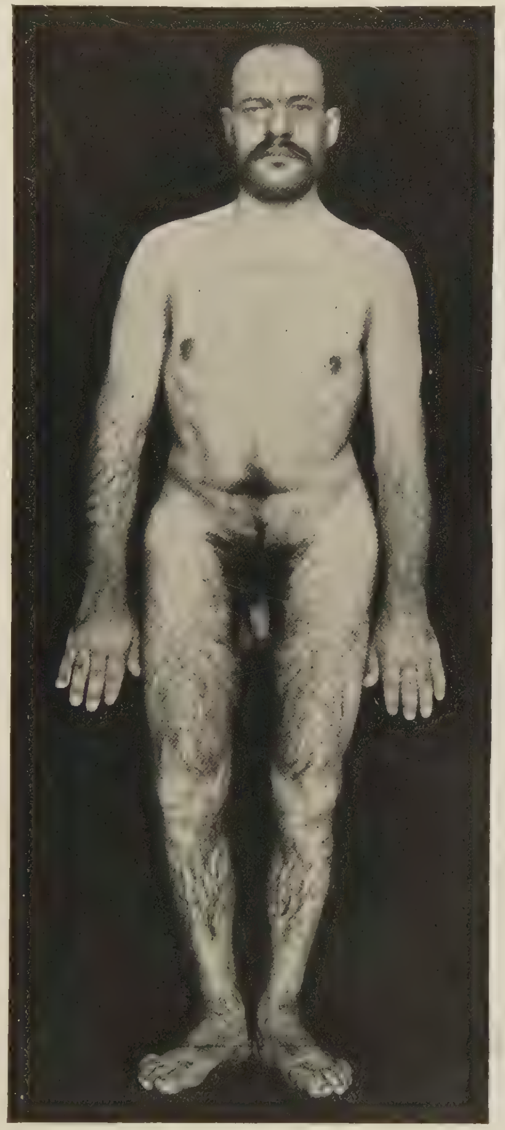

Fig. 36.—Abnormally strong growth of hair in acromegaly (Observation XXV).

Also in the skin are found, especially in the sacral parts, sclerotic processes affecting both the epidermis and cutis parts. The papillæ are enlarged, and the sclerosis extends to the nerves and vessels and to the connective tissue fasciculæ surrounding the glands. Frequently abnormal pigmentations are found. In spite of sclerosing processes the skin may be readily raised up in folds, which fact is important in the differential diagnosis from myxedema. In the later stages true myxedematous alterations of the skin are found not rarely (see below).

*Pierre Marie* found mollusca pendula in numerous cases. The secretion of

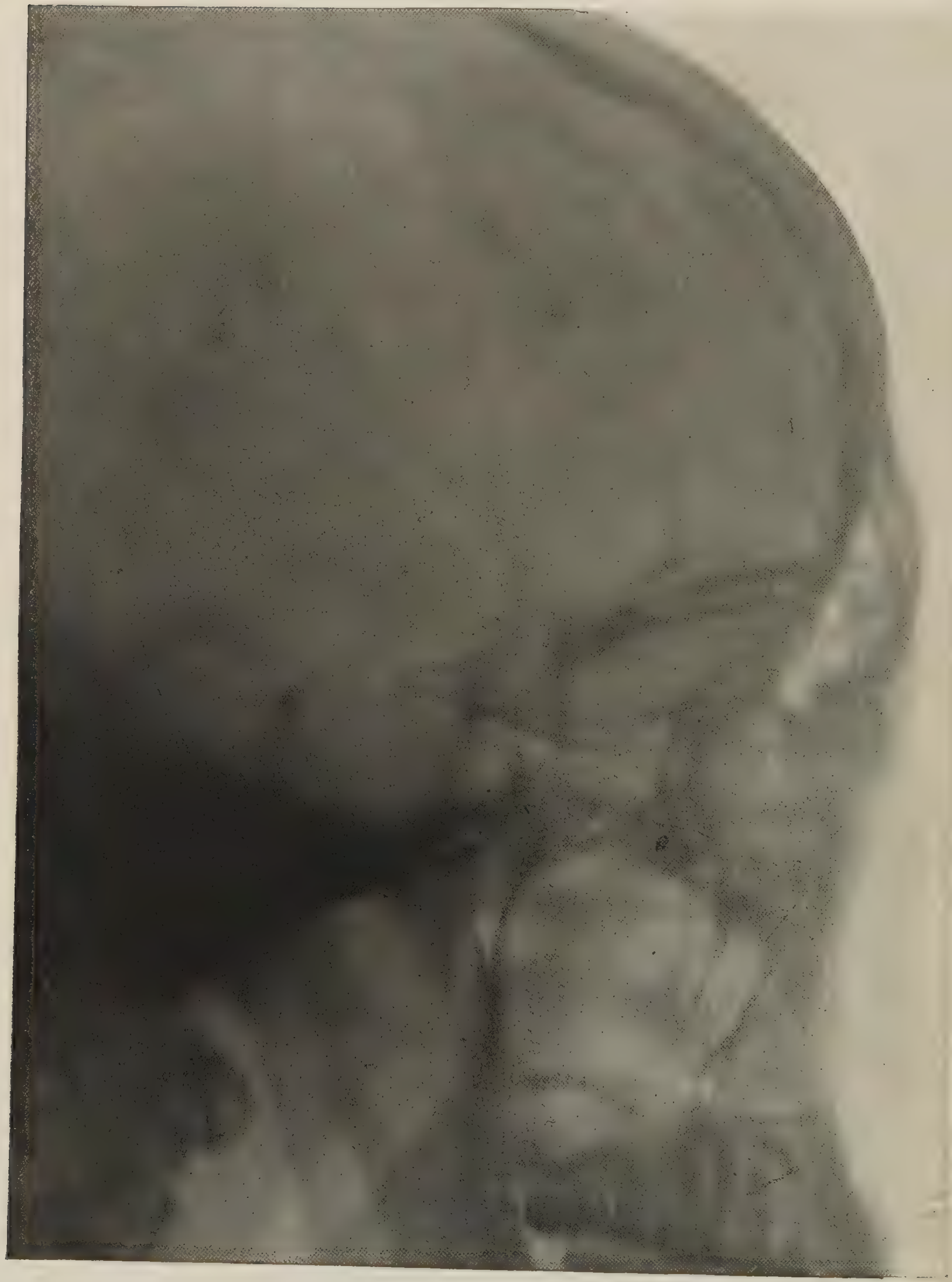

FIG. 37.—Widened sella turcica in acromegaly (Observation XXV).

the sebaceous glands is increased (see below for information concerning increased sweat secretion).

The *growth of hair* on the head is often remarkably dense, and the individual hairs are thick. In the course of the disease abnormal hair growth occurs on the trunk and extremities, as may be seen in the following observation.

*Observation XXV.*—T., thirty-one years old, cobbler, entered the clinic Dec., 1911. First admitted Nov. 16, 1905. Since 1903 gradual enlargement of the hands. All military gloves were too small for him. Also face has become broader, nose and lips have become larger, weight somewhat less. Headache, pigmentations of the skin, thyroid slightly enlarged. Eye-grounds normal. No hemianopsia. Sella turcica uniformly enlarged to the size of a cherry. The dorsum sellæ thinned. The clinoid processes pushed backward. Skeleton of the hands and feet show appreciable thickening of the soft parts.

Nov., 1907. Headache has become much more severe. *The hairiness of the body has increased markedly.* The hairs are brittle. *Marked hairiness of the genitalia, abnormal hairiness of the abdomen and extremities.*

Arcus superciliares enormously developed. Nose enlarged. Lower jaw slightly prognathous. Cushion-like ear lobules. *Mustache bristly.* Hairiness of the linea alba very strong. Very deep wrinkle formation on forehead. *Potency entirely normal.*

Sella turcica deepened three times more than is normal. Dorsum sellæ much thinned and elongated.

Alimentary glycosuria negative.

Dec., 1911. *During the last year the hairiness has become even denser. Libido is unaltered, the potency has decreased slightly.* Typical acromegalic alterations of the skeleton and the soft parts, no tachycardia. Slight enlargement of the thyroid gland.

Investigations of the Exchange of Gases (*Dr. Bernstein*).

| | | | Per kg. of body weight | |
|---|---|---|---|---|
| $CO_2$ | $O_2$ | RQu | $CO_2$ | $O_2$ |
| 233.5 | 288.7 | 0.809 | | |
| 275.5 | 342.0 | 0.753 | 2.733 | 3.55 |
| 266.7 | 329.8 | 0.748 | | |

Alimentary glycosuria strongly positive (0.78 gm. dextrose)

Erythrocytes, 4,490,000
Hemoglobin, 95 per cent.
Leucocytes, 4900, of which:
Polymorphonuclear neutrophiles, 56.7 per cent.
Lymphocytes, 30.5 per cent.
Large mononuclears, 12.6 per cent.
Eosinophiles, 0.2 per cent.

Investigation of the elimination of uric acid on purin-free diet shows values between 0.72 and 0.97 gm.—therefore is very appreciably increased.

The following is an additional example of abnormal hairiness in acromegaly.

*Observation XXVI.*—I. Bo., thirty-one years, entered May, 1911. The sickness began in 1905. First enlargement of the fingers, then, about simultaneously, enlargement of the feet, the skull, the nose, the neck. In 1908 began enlargement of the lower jaw. Also the ears became somewhat thickened. Since 1909 the forearms and the metatarsus too have grown. Also the circumference of the chest has increased and the *hairiness of the trunk* has become essentially stronger. Number of collar formerly 41, now 46. For two or three years on every psychical excitement, and less on every bodily movement, *in-*

*stantaneous occurrence of outbreaks of sweats; potency not entirely normal* since the age of twenty, since the beginning of the disease rapid diminution of libido, and now it is lost utterly. Appetite increases at times. In 1910 *thyroidin administered at home; this led to palpitations of the heart, that have persisted to the present. Thyroidin also acted unfavorably on the sweats.* A cousin of his father's also suffered from acromegaly. For six or seven months headaches on the vertex and occiput. Power of attention has considerably decreased. Often cramps of the musculature of the feet, and calves, and sticking pains in the bones of the hands and feet.

Moderately compact body build. Head enormously big. Orbital margins protrude. Root of nose very much broadened. Nose very thick, lower jaw extraordinarily massive.

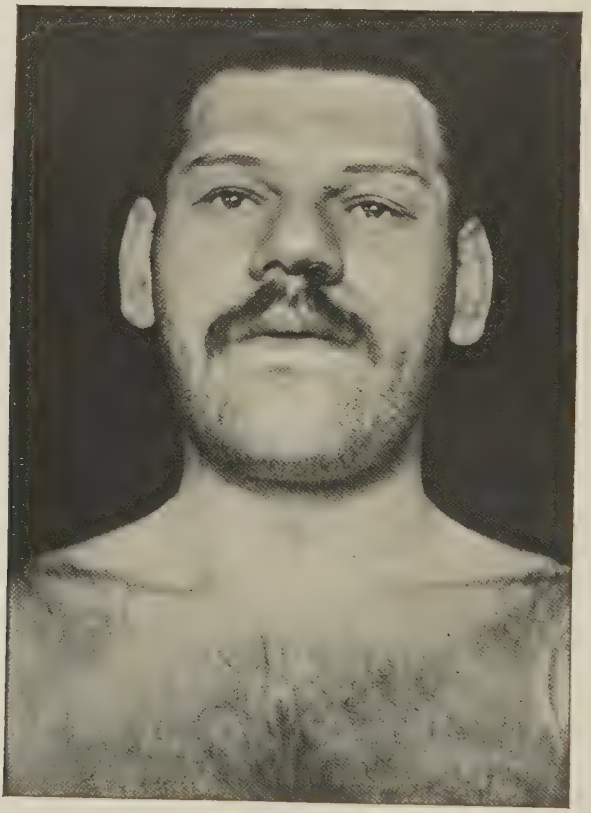

FIG. 38.—Case of acromegaly (Observation XXV).

Lower row of teeth about 2 cm. forward; the teeth of the lower jaw stand far apart from one another. The color of the face is pale. Hair of the head dense and turns gray easily. Circumference of the skull 62.5 cm. Circumference of the neck 45 cm., larynx enlarged. Thyroid gland not enlarged. *Enormous growth of hair on thorax.* Circumference of the thorax 107 cm. on inspiration, 97 cm. on expiration. Large erectile nipples.

Pulse 56. Extremities enormously thickened in the distal parts.

For example. Circumference of each thumb 8.5 cm., circumference of middle finger 8.5 cm.

Erythrocytes, 5,210,000
Hemoglobin, 85 per cent.

Leucocytes, 8840, of which:
Polymorphonuclear neutrophiles, 63.8 per cent.
Lymphocytes, 29.7 per cent.
Large mononuclears, 4.2 per cent.
Eosinophiles, 2.3 per cent.
Alimentary glycosuria (100 gm. dextrose) negative.
Pituitrinum infundibulare (2 cc.) no influence on diuresis, no glycosuria.

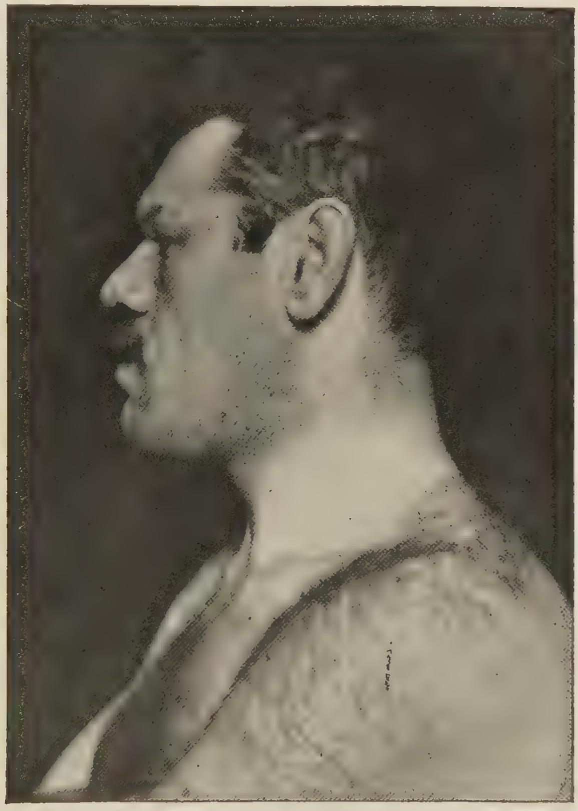

Fig. 39.—Abnormally strong growth of hair in acromegaly.

X-ray examination (*Docent Schüller*) skull thick with enormous frontal sinuses. Sella markedly widened, dorsum sellæ lengthened, coarse, reclining, anterior clinoid process broad, no sphenoidal sinuses.

Eye examination (*Prof. Sachs*). Vision and field of vision normal.

Operation was undertaken by *Dr. Hirsch* on May 29, under local anesthesia, by the endonasal route. For the details I refer to *O. Hirsch's* publications. The cavity made in the hypophysis by operation reached about 2½ cm. in the sagittal and 1½ cm. in the vertical diameter. The temperature rose to 38.0° transitorily, falling back to normal in a few days. On June 2, the patient already made the observation that the size of the end-phalanges of the fingers had decreased. There must also have occurred a diminution in the size of the feet, as the slippers that were formerly too small, now fit him. On June 3, the patient observed that his hat, that also had been too small, now fell down on his forehead. On June 9, an improvement in the attention became apparent. The patient, who was a doctor of mathematics, could, before the onset of his illness repeat all of 12 two-digit figures that were told to him at intervals of five seconds. Before the operation he could remember only 7. Now he regularly repeated 11. June 11, the greatest circumference of the head which before the operation reached 62.5 cm., is now 61.4 cm. The greatest circumference of the neck, formerly 46 cm., now is 43 cm. The water displacement of the hands which formerly was 700 cc. is now 600 cc. The thickenings about the eyes have now retrogressed, and the soft parts of the cheeks and chin have also distinctly fallen off. On June 19, the patient left for his home.

Histological examination of the material obtained on operation (*D. Erdheim*) showed an adenoma consisting in small round cells that look alike, with round vesicular nuclei and a well-developed protoplasm; at regular intervals the tissue is permeated with bloodvessels with capillary walls, giving to the tumor a trabecular, in some places an alveolar, appearance. At places proliferation and hyaline degeneration of the stroma, often with extensive hemorrhage. I mention briefly, from the patient's report in July that the sweats have improved considerably, from his report in August that the circumference of the head has decreased still more, the thirst has subsided, but there has been no alteration in the vita sexualis. In January, 1912, he reported that retrogression of the acromegalic manifestations had not gone further; that lately even an aggravation had set in, this consisting in the fact that the tongue had become thicker, the mental attitude was that of depression, the thirst had again become greater, but there was no more polyphagia.

Often too the eyebrows became bushy. In women often hairs develop on the upper lip, and bristly hairs on the chin and on the lower lip, similar to the chin-beard in man, also hairs on the cheeks, and especially on the inner side of the thigh and even on the linea alba (also a case of *Stumme's*). This occurrence of abnormal hairiness in women is illustrated by the following case:

*Observation XXVII.*—E. T., thirty-three years, entered Nov., 1909. Menstruated first at the age of twelve years, followed regularly at intervals of four weeks, the flow lasting eight days, profuse. Lues at the age of nineteen years, primary sore on the left labium minor, twelve injections, after six weeks papules in the genitals, nineteen inunctions. The end of 1895, an abortion, and 1898 apparently a purulent parametritic exudate, 1907 another abortion.

The present illness began in 1902 and within one-half year had attained almost its present intensity. First paresthesias in the upper extremities and shoulders, then thickening of the fingers, so that the patient had to discard her rings. A half year later enlargement of the feet, so that the shoes became very much too small. At the same time occurred enlargement of the lips and nose. The circumference of the neck had increased about 4 cm., the abdomen also became thicker, *and hair began to grow on the breast and calves.* The breasts did not become especially larger, but *milk began to be secreted by them.* Periods extremely irregular, at one time remained away for seventeen months, *libido at first increased, then diminished.* The voice right at the onset became deeper. Lately frequent outbreaks of sweat. Occasional voracious hunger and great thirst. Often frontal headache.

Typical acromegalic appearance. Hands and feet enormously large. Skin very moist, *marked hairiness of both arms, hairs between the breasts and on the genitals, the hairs of the mons veneris reach as high as the navel.* Hairiness therefore that of a man. *Circumanal and perineal hairs abundant. Also the leg is markedly covered with hair.* Nose and lips makedly thickened, lower jaw protrudes rather strongly. The incisor teeth of the lower jaw are far apart from each other. Tongue very much more enlarged. Thyroid enlarged. *Colostrum can be expressed from the breasts on light pressure.* Eye-grounds and field of vision normal. Lordosis of the lumbar spine. Enlargement of the nose and lower jaw, hands, and feet. X-ray: Sella turcica much widened, as big as a crown piece. The posterior clinoid process consumed.

Dec. 3—100 gm. dextrose—3.58 gm. dextrose in urine. On a purin-free diet the values of uric acid were 0.765, 0.720, 1.204, 1.296, 1.050, 1.097, 1.080, 0.762, 1.155, 1.011, 0.855

Blood examination erythrocytes, 4,975,000
Hemoglobin, 12 gm.
Leucocytes 5600 of which:
Polymorphonuclear neutrophiles, 76 per cent.
Lymphocytes, 22 per cent.
Eosinophiles, 2 per cent.

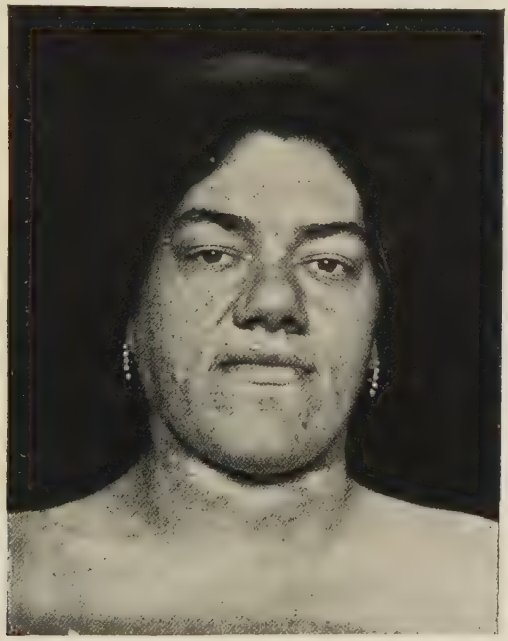

FIG. 40.—Case of acromegaly.

Dec. 8—0.001 gm. adrenalin subcutaneously. Pulse gradually rose from 72 to 102. Blood-pressure from 95 to 115. After twenty minutes return to normal. Slight headache, tremors, slight arrhythmia, considerable increase in diuresis, no sugar.

Abundant carbohydrate diet leads to glycosuria.

Dec. 14—0.001 gm. adrenalin subcutaneously. Pulse from 72 to 96, blood-pressure from 115 to 125, slight headache, slight arrhythmia, no sugar, diuresis from 950 to 2000.

Dec. 15—1 cc. pituitrinum infundibulare, marked diuresis, no sugar.

Dec. 16—100 gm. dextrose, sugar strongly positive.

Dec. 17—100 gm. dextrose, in urine 2.1 gm. dextrose.

Dec. 21—0.01 gm. pilocarpine, moderate sweating, moderate flow of saliva.

Very noteworthy in acromegaly are alterations in the genitalia, that is, the manifestations that may be ascribed to functional alterations of the sexual glands. We shall see later that for the comprehension of especially the genital disturbances in acromegaly and for the pathogenesis and theory of acromegaly in general there seems necessary a sharp distinction between the function of the interstitial glands and the generative glands, at least so far as this is possible, according to our present-day knowledge. As will be seen from the description of the alteration in the hairiness, which I have just completed, there is almost never found in this condition a retrenchment of the so-called secondary sexual characters and a retrogression of the external genitalia. An exception to this is perhaps certain cases of acromegaly in childhood, which I shall speak of in detail later. In acromegaly of adults, on the contrary, there is mostly sharp accentuation of the secondary sexual characters. As has been mentioned there is often seen a strikingly strong development of the hairs of the beard; the axillary hairs, the hairs on the genitalia and on the perineum grow more strongly, and often there develops a marked hairiness along the linea alba; the hairiness in women, as *v. Noorden* mentions, often assumes in this case a virile type. Moreover the external genitalia often show a distinct hyperplasia. The penis, the labia majora and the clitoris may appreciably increase in dimensions.

These phenomena persist until the end of the disease. In certain cases we can at least say that a distinct retrogression does not occur.

The function of the glands of generation behaves otherwise. Here we mostly find premature lessening or loss of function. There are, however, numerous exceptions, that I shall speak of first. At the beginning of the disease there is found not at all rarely signs of the increased function. Thus there was for instance, in the case of *Buday* and *Janczo* (acromegalic gigantism) increased potency at the beginning.

Also in women, libido may be increased at the beginning; I here allude to Observation XXVII. In this case the illness had lasted seven years; in spite of this menstruation, although irregular, persisted; the libido was at first increased, later decreased. Colostrum could be expressed from the breasts. Cases of persistent galactorrhea have been described by *Gajkievicz* and *Fazio*. In other cases the function of the glands of generation last until in the fully developed disease. I refer to Observation XXV. In this case the disease began in 1903, in the year 1907 the potency and libido were entirely normal, 1911 the libido was as yet entirely retained, but the potency had to a certain extent diminished.

In such cases signs of increased activity of the sexual glands may be found at autopsy. Thus *Schultze* and *Fischer* state that in a man aged fifty-six (Case 2) in whom the acromegaly had lasted seven years, strikingly abundant spermatogenesis was to be found in the testicles, and the prostate was enlarged and in a condition of abundant secretion.

The following case, although not so instructive, seems a further example of the preservation of the generative function:

*Observation XXVIII.*—F. Da., thirty-eight years old. Ambulant patient in 1911. For nine years married, three children. Wife has had one abortion; for about one and one-half years the hands and feet have become thickened, etc. Collar number has risen from 41 to 44, hat number from 55 to 58½. One year ago the incisor teeth spread apart from each other, and the lower jaw projected. Often polydipsia. Dyspnea on ascending stairs. More readily excited than formerly. Body weight has increased from 7 kg. to 83 kg. Arching of the chest has increased. *Potency not altered.* Typical acromegaly. External genitalia strongly developed, large amount of hair on them.

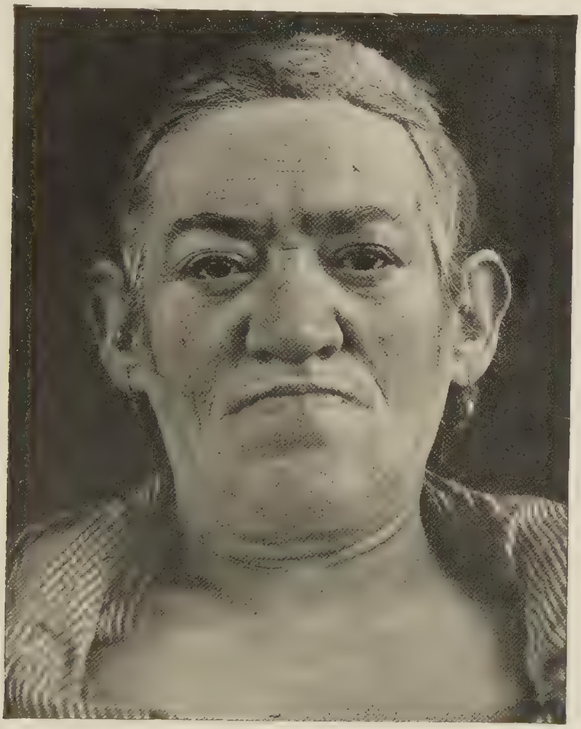

FIG. 41.—Case of acromegaly (Observation XXIX).

Erythrocytes, 5,300,000
Hemoglobin, 90 per cent.
Leucocytes, 8100, of which:
Neutrophiles, 74 per cent.
Lymphocytes, 20 per cent.
Eosinophiles, 6 per cent.

Test as to alimentary glycosuria (100 gm. dextrose)—in urine 1.3 per cent. = 0.88 gm.

Eye findings normal, sella turcica almost the size of a gulden piece.

Also menstruation may be present for a long time in acromegalic women. In *Becker's* case the menstruation ceased as late as eighteen years after the beginning of the affection; in a case of *Döbbelin* there was entirely normal genital function. A short time ago I even saw a case in which the likelihood had to be considered that in a course of a very chronic acromegaly conception had occurred several times, and children had been carried to term. I here quote the case in extenso:

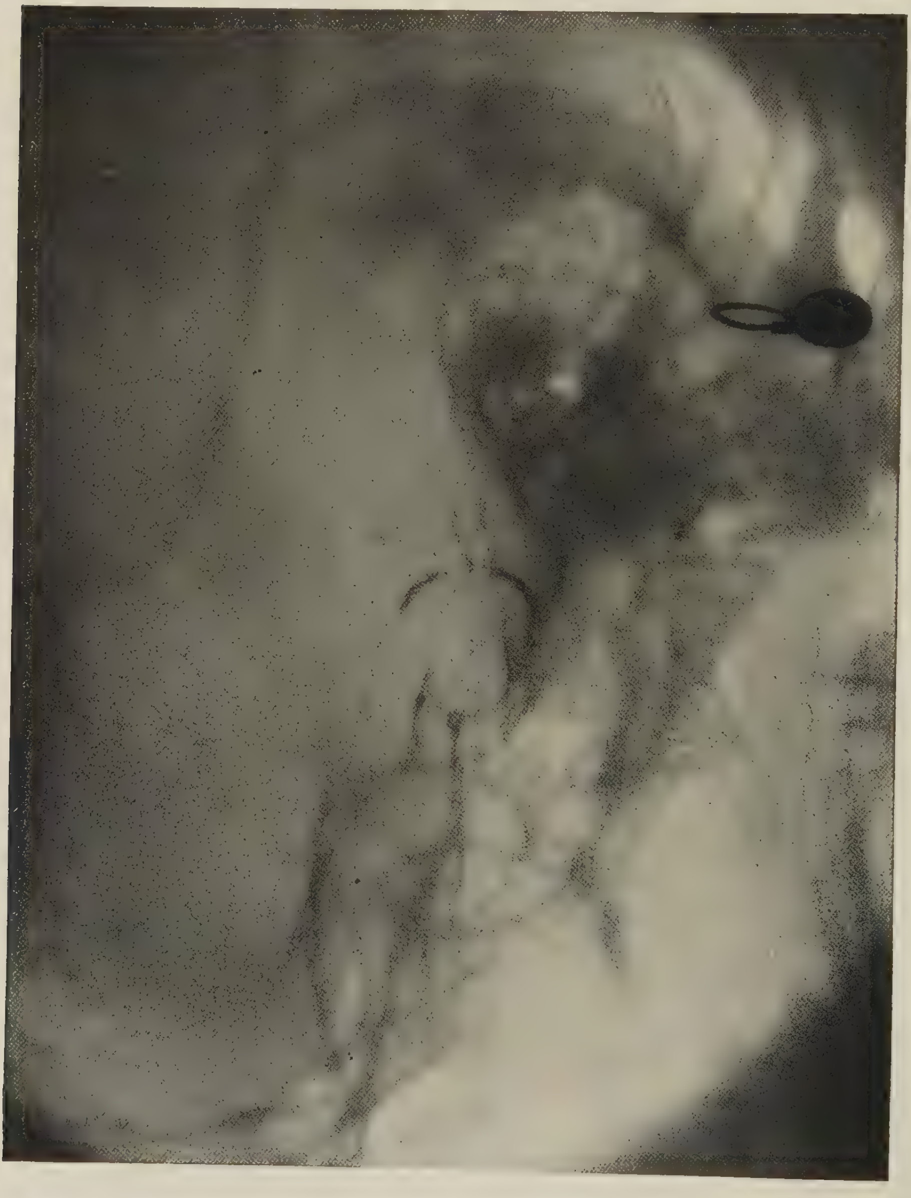

Fig. 42.—Widened sella turcica (Observation XXIX); neighborhood of sella retouched.

*Observation XXIX.*—S. Ad., fifty-six years old. Entered the clinic Oct., 1912. The father of the patient seems to have been rather vigorous and in his later years his condition seems to have exhibited some resemblance to the patient. From the age of fifty-six years on his face became broader. He died of pneumonia in his seventieth year. No ductless glandular diseases in the family. The patient has seven brothers and sisters, all well. She has five children, the first child born when she was in her twenty-eighth year, the last when she was in her fortieth year. All the births were normal, and all the children were well developed. Menstruated first at the age of twenty-two years, the menses were always rather profuse, lasting two to three days, and occurring regularly every four weeks, menopause at the forty-sixth year. For two years headaches, especially at the roof of the skull of the right side, which headaches have increased in intensity. The pains now exist day and night and for the most part are so intense that the patient cannot sleep. During the last four to five months she has always remained in bed on account of these headaches and on account of the fact that when she attempted to get up she would suffer with attacks of vertigo. The patient had also had headaches for some time before this but she did not give them much attention. She states definitely that the enlargement of the hands and feet developed gradually between the twentieth and thirtieth year of life. At the time of the birth of her first child in her twenty-eighth year the hands and feet were much larger and thicker than at present, and have gradually decreased in circumference. Also the prognathism of the lower jaw has existed since that time. She never suffered from sweats or from pains in the extremities.

The patient looks at least fifteen to twenty years older than she is. Height 145.5 cm., span width 150.5 cm. Layer of fat well developed. Skin pale, smooth and dry, musculature weak, build of bones medium, considerable kyphosis; the extremities are extraordinarily heavy, head large, fronto-occipital circumference 56 cm., nose large with broad insertion; distance from between the eyebrows to the tip of the nose 5.8 cm.; breadth of the nose 4.5 cm., distinct prognathism. From temporomaxillary joint to temporomaxillary joint, over chin, 26 cm. Lower lips thick, cushiony and prominent. The teeth are in greater part absent, the two lower incisor teeth are present and are spread apart from each other. The clavicles are rather broad; the extremities extraordinarily awkward. The fingers are markedly thickened and the X-ray shows that the thickening affects the weak spots exclusively. The metacarpal bones are pushed apart from each other, only very slight bone formation at the seat of the muscular insertions. Also the feet are awkward. Axillary hair and pubic hair well developed. Isolated hairs on the upper lips. Slight arteriosclerosis.

Alimentary glycosuria (100 gm. dextrose), 0.8 gm.
Blood findings: Leucocytes, 9800, of which:
Polymorphonuclear neutrophiles, 66 per cent.
Lymphocytes, 30 per cent.
Large mononuclears, 3 per cent.
Eosinophiles, 1 per cent.

One week later repetition of the test for alimentary glycosuria after injection of twice 4 cm. pituitrinum glandulare intramuscularly (100 gm. dextrose) 0.9 gm.

X-ray examination of the skull (*Dr. Schwarz*): Widening of the sella turcica to the size of a 2-crown piece. Deepening of the floor of the sellæ, processus clinoidei sharpened. Entrance to the sellæ widened.

Eye examination (*Docent Ulbrich*) papillæ normal, the inner borders slightly effaced and slightly prominent. Nothing certainly pathological; on the contrary, vision O. D. 3/36, O. S. 1/36, but there is an old trachoma with corneal scars; visual field on each side, so far as can be tested, normal; also normal for colors.

The examination of the uric-acid elimination on purin-free diet shows values between 0.4–0.5 gm., therefore no increase.

As far as I have been able to find, a similar case of conception in acromegaly has been reported only by *Pirie.*

However, in the great majority of cases of acromegaly, as has already been mentioned, there occur sooner or later signs of extinction of the function of the generative glands. This may occur even early, constituting a differential diagnostic difficulty. In man there soon comes to pass lessening or complete loss of potency and libido, and in woman amenorrhea. As the latter is attended with a cessation of ovulation, it may very well be supposed that as yet no case of conception has been observed in an amenorrheic acromegalic woman.

In such cases the sexual glands and the internal generative organs gradually atrophy. *Tandler* and *Grosz* found total retrogression of the primordial follicles and cessation of the formation of *Graafian* follicles, and in man alteration of the epithelium of the seminal tubules and, finally, also alteration of the interstitial cells. On gynecological examination the uterus is usually found to be small. Not rarely cystic degeneration of the ovaries is also present. Atrophy of the internal genitalia was found in 36.4 per cent. of 118 cases, according to the statistics of *Creutzfeldt.*

That even on long-continued amenorrhea the follicular apparatus may not degenerate entirely is shown by a case of *Cagnetto;* menstruation ceased at the age of nineteen years; at the age of forty-six years it reappeared and continued to the age of forty-eight years, when it disappeared for good; autopsy showed cystic degeneration of the tumor of the pituitary; in this case it is not unlikely that the hyperfunction was restricted by the cystic degeneration.

We may therefore briefly sketch the relation between hypophysis and sexual glands, thus: increased activity of the hypophysis stimulates the activity of the interstitial glands (apparently also the suprarenal cortex). The glands of generation are sometimes first also stimulated to increased activity, but for the most part the activity is suspended. Conversely we find that on increased activity of the sexual glands there is also increased activity of the hypophysis. During pregnancy I assume in opposition to the prevailing teaching that there is in pregnancy an increased activity of the sexual glands, as I regard the developing fetus as a prolonged ovulation (see chapter on the sexual glands)—there is found enlargement of the hypophysis and signs of an increased function of that organ, coarsening of the facial features, etc. (*Tandler* and *Grosz*). Indeed the transitory acromegaly may even occur during this period. Such a case is reported by *R. Marek.* Pronounced acromegalic symptoms occurred during pregnancy in a twenty-seven-year-old primipara. Nose, tongue, and jaws became larger, the teeth spread apart, the hands and tongue increased in circumference, the tonsils swelled, glycosuria, lassitude, sleeplessness and insomnia, and also drawing pains in the muscles made their appearance. All signs disappeared during the puerperium.

In such cases of formes frustes of acromegaly during pregnancy, we may think very plausibly of an existing predisposition; we might also be inclined to believe that repetition of the pregnancy would lead to permanent manifestation of the disease.

*Goiters* and *alterations in the function of the thyroid* occur in acromegaly with great frequence. The development of the goiter may occur about simultaneously with that of acromegaly, and thus symptoms of hyperthyrosis or hypothyrosis may become manifest simultaneously with acromegalic symptoms. Manifestations of a slight hyperthyrosis in acromegaly are especially common. *Magnus-Levy* and *Salamon* have especially directed attention to this subject. Later, in the consideration of the manifestations on the part of the vegetative nervous system, we shall see that among the more frequent symptoms in acromegaly are sweats. We shall have to study, however, whether we are justified in regarding them as a symptom of a simultaneous hyperfunction, and whether they do not signify rather that certain organs of supply of the vegetative nervous system are not directly influenced by the irritation of these nerves, on account of the hyperfunction of the hypophysis. A tachycardia might be regarded as a surer symptom of hyperthyrosis especially when there exists thyroid swelling and increased fall in blood-pressure.

In case U (Observation XXIV) the thyroid was enlarged. There existed profuse sweats and a slight grade of tachycardia. Slight enlargement of the thyroid was present also in case T, Observation XXV, but in this case symptoms of hyperthyrosis were not distinct.

Of the remaining symptoms of Basedow's the following have been stated to have occurred in the course of acromegaly: tremor, transitory rises of temperature, cardiac palpitation, increased psychical irritability.

The following is a very instructive example of the simultaneous development of acromegaly and a slight hyperthyrosis.

*Observation XXX.*—M. St., thirty-seven years old. First admission at hospital in December, 1896. Menses appeared first at the eighteenth year, and were regular up to the twenty-fourth year of life. From then on they remained *absent.* At the thirty-first year *tearing pains in all the members appeared,* especially at night. The fingers were swollen, and there were sometimes intense sensations of heat. Since that time there have existed severe headaches. Finally there *developed* about this time *a goiter.* In addition *there appeared pains in the neighborhood of the thyroid gland, which recurred every month.* Lately forgetfulness, lassitude, and weakness. The motor power has weakened.

Typical acromegaly and thickening of the nose, hands and feet. Circumference of the throat 44 cm. Slight degree of anemia. (Hemoglobin 65 per cent., erythrocytes 4,000,000.) *Enormous struma of the thyroid, both lobes diffusely enlarged, with circumscribed nodules,* no hemianopsia, no disturbances of vision. Slight kyphosis.

Second admission, March, 1892. Now marked kyphoscoliosis. The acromegaly has advanced.

Third admission, August, 1899.

Fourth admission, December, 1899. *Fine tremor, exophthalmus, tachycardia, marked alimentary glycosuria* 2.25 per cent. dextrose in urine when 100 gm. dextrose administered.

To 100 gm. *levulose, Trommer* transitorily distinctly positive.

Fifth admission, May, 1907. For two years there has been a gradual diminution in the motor power. Goiter seems to be smaller. Appreciable enlargement of the sella turcica. The enlargement of the hands depends only on the enlargement of the soft parts. Frontal cavities enormously widened. Eye-findings normal. *Alimentary glycosuria* (50 gm.) now *negative*. Death from pneumonia.

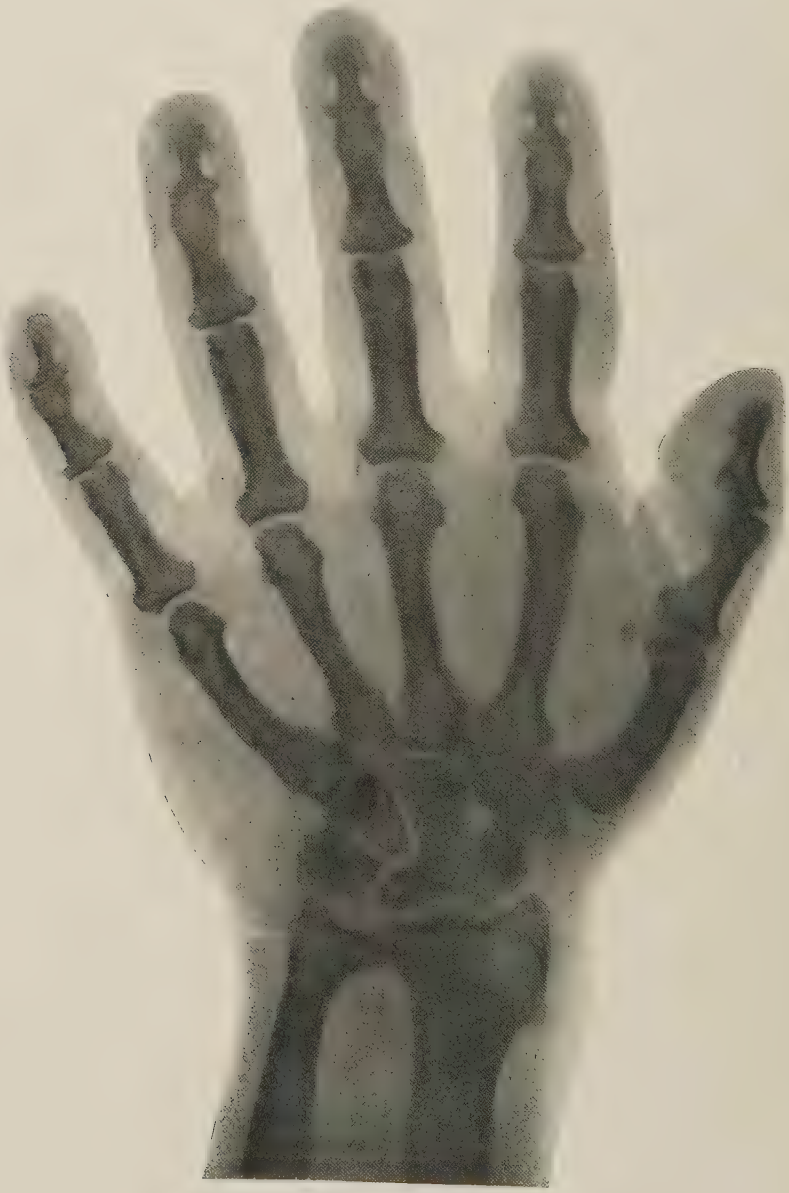

FIG. 43.—X-ray picture of the hand in acromegaly (½ natural size).

*Autopsy.*—Tumor of the hypophysis of soft confluent consistence and grayish-red color. Besides, in various organs, numerous tuberculomata.

In this case then in the thirty-first year of life the goiter appeared simultaneously with acromegaly; the goiter subsequently developed enormously and led to pronounced symptoms of hyperthyrosis (tremor, exophthalmus, tachycardia, etc.). Also the alimentary glycosuria could have been a symptom of the hyperthyroidism, at least it disappeared later, when the goiter became re-

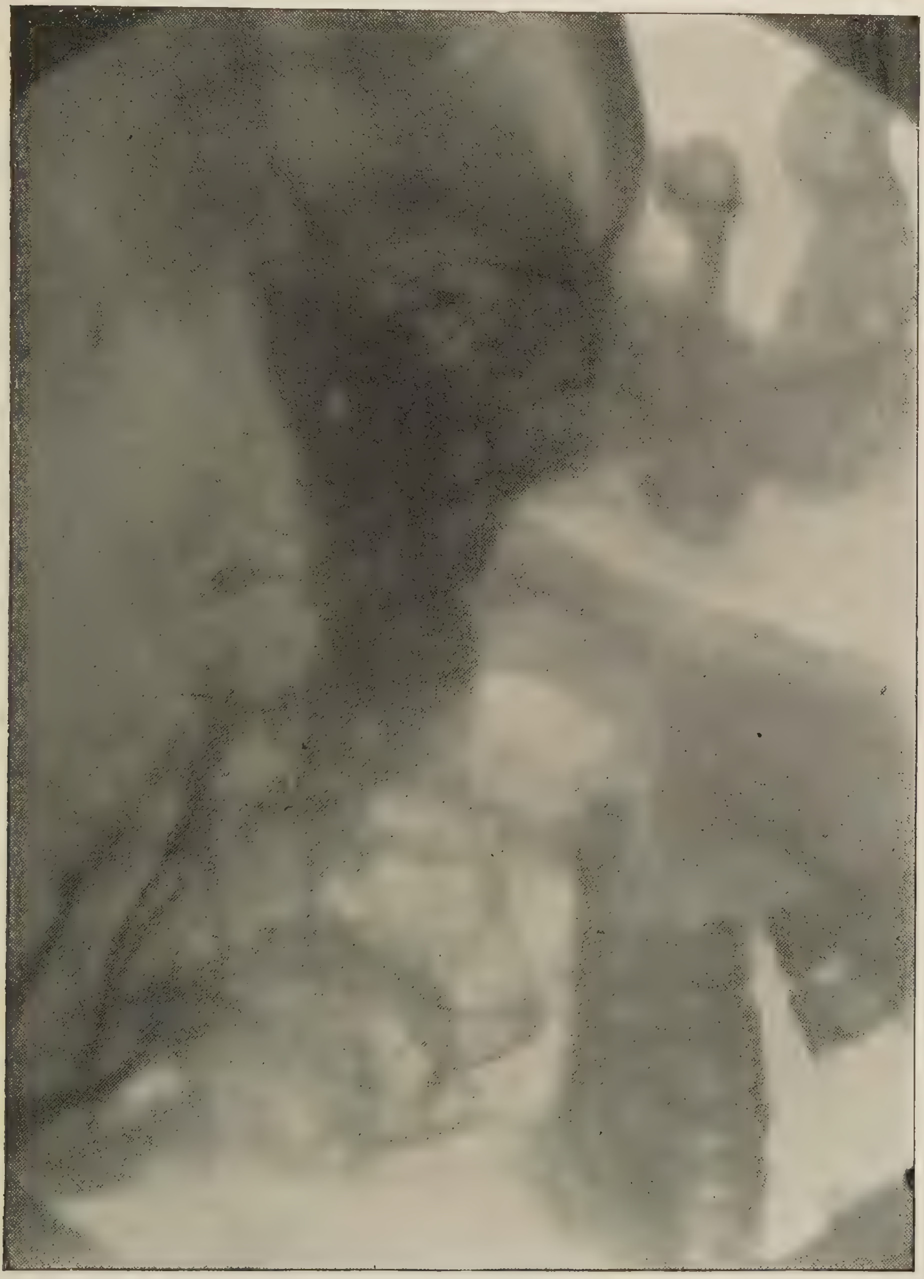

Fig. 44.—Dilated sella turcica in acromegaly (Observation XXX).

duced. Such a retrogression of a preceding goiter occurs frequently in the later stages of acromegaly. With its disappearance may be associated not only a disappearance of the Basedow's symptoms, but also, as in this case, the appearance of symptoms of true myxedema.

*Observation XXXI.*—A. Str. First entered the clinic in February, 1896, then thirty-one years old.

Chlorosis at the age of eighteen years. Menstruated first at the age of fifteen years; menstruation was regular until her marriage in her twenty-first year. Pregnancy and delivery normal, child well. *Since that time has never menstruated*, and has become progressively weaker. Two years after the confinement (1898) the hands and feet began to become thicker and coarser, the wedding ring had to be filed off and enlarged, and it had to be made even larger in 1890 and 1893 respectively. Also the shoes had to be made larger. Also the rest of her body became always thicker and more awkward, the neck became swollen, but the breasts became progressively smaller. The facial features altered more and more so that at times she was not recognized as herself by good friends. In spite of the increase in body she became progressively weaker. Burning pains in the fingers occurred early in the course of the disease, pains that were increased at night by the warmth of her bed. Later were added *day-sweats and night-sweats*, so that night-clothing and bed-linen had to be changed several times during the night. The eyes protruded distinctly. Occasionally she had headache and vertigo. Speech became rough and nasal, the tongue has become heavier, thicker and longer, so that it was often caught by the teeth when she spoke. Formerly set of teeth was quite regular. At present the anterior incisor teeth of the lower jaw incline outward, are spread apart from each other, and do not fit those of the upper jaw. At first she suffered with constipation; often there was no evacuation for fourteen days, latterly she often has *diarrheas*. She is very nervous, and frequently has cardiac palpitations and difficulty in breathing. Slight tremor. The powers of memory have suffered, the [mental] *attitude is depressed and she is easily excited.*

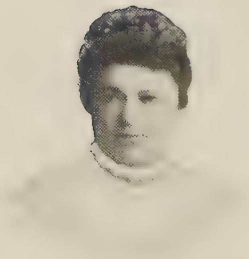

Fig. 45*a*, before the disease.

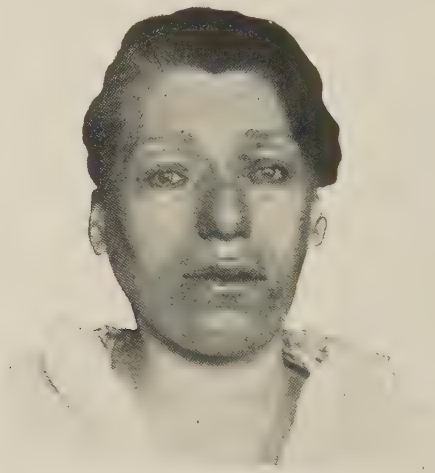

Fig. 45*b*, at the height of the disease.

Case of acromegaly.

Circumference of skull, 57.7 cm.

Length of nose, 5.5 cm.

Distance apart of the alæ of the nose, 4.2 cm.

*Circumference of the neck*, 40.0 cm.

Circumference of the waist, 86 cm.

Height, 163 cm.

Eye-grounds and perimetry normal.

Second entrance, January, 1901. There now exist slight swellings of certain joints, especially of the knee and elbows, where crepitation is present on palpation. The cardiac oppression has become intense. The voice seems to have improved. The distance between the middle and upper incisors is now about 1 mm., that between the lower middle incisors 9 mm. The tongue is enormous; hands and feet have greatly broadened. The tubera parietalia project markedly, and does also the arcus superciliares; alæ of the nose, the lips and lower jaw have enlarged enormously. The spinous processes are sensitive to pressure. Also pain in the entire vertebral column is elicited by pressure on the head. Eye findings normal. *The circumference of the throat has increased about 3 cm.*

Third entrance to clinic, January, 1903. Attacks of frontal headache with insomnia. Alimentary glycosuria, a trace of sugar on the ingestion of 100 gm. dextrose.

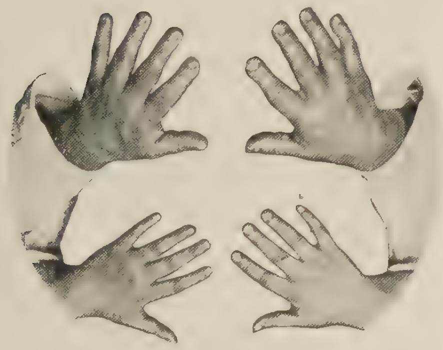

FIG. 46.—Acromegalic and normal hands.

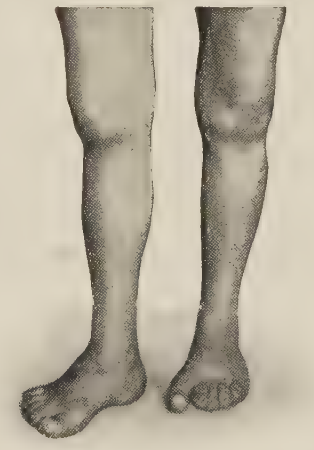

FIG. 47.—Acromegalic feet.

Gynecological examination: Flat pelvis with very slight osteomalacic changes. Painfulness of the bones, *Chvostek's* phenomenon positive.[1] One time it was possible to elicit *Trousseau's* sign.

Flexion of the hip- and knee-joints much restricted. Spasms of the adductors. The knee-joints greatly distended, crepitation. Electrical irritability normal. Eye findings normal.

Erythrocytes, 4,278,000

Hemoglobin, 10.2 gm.

Leucocytes, 2900, of which:

Polymorphonuclear neutrophiles, 6 per cent.

X-ray: Skull capsule thickened. Sella turcica irregularly widened, clinoid processes hyperostotic. The thickening of the extremities affects the soft part exclusively. The bones are atrophic.

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[1] On account of these manifold symptoms, the case was exhibited by *A. Müller* before the Wiener Gesellschaft f. innere Medizin und Kinderheilkunde.

Fourth entrance to the clinic, April, 1909. *Copious night-sweats, cardiac palpitations. Circumference of the throat* 38 *cm.* Alimentary glycosuria negative.

*Pigmentation on the face, hands and neck* 0.001 gm. adrenalin subcutaneously, no sugar.

Fifth entrance to the clinic, November, 1909. *Circumference of the neck* 35 cm. Heart enlarged, extra systoles; *Chvostek* negative.

Sixth entrance to the clinic, April, 1910. Alimentary glycosuria (100 gm.) negative. Adrenalin 0.001 gm., no sugar.

Three thyroidin tablets administered thrice daily for three days, the pulse rate was somewhat increased. Cardiac palpitations slight, the neutrophilic leucocytes are from 71.5 per cent. to 84 per cent. Alimentary glycosuria after the beginning of thyroidin medication negative (confer *Falta*, *Newburgh*, and *Nobel*).

X-ray: The sella turcica is destroyed to the extent that its site is no longer sharply delimited below and in front; it has given place to a cavity about the size of a chestnut. The anterior clinoid processes are replaced by washed-out bone masses; this is true also of the greater part of the floor, especially anteriorly. The somewhat enlarged clivus projects forward as a characteristically nipple-shaped mass.

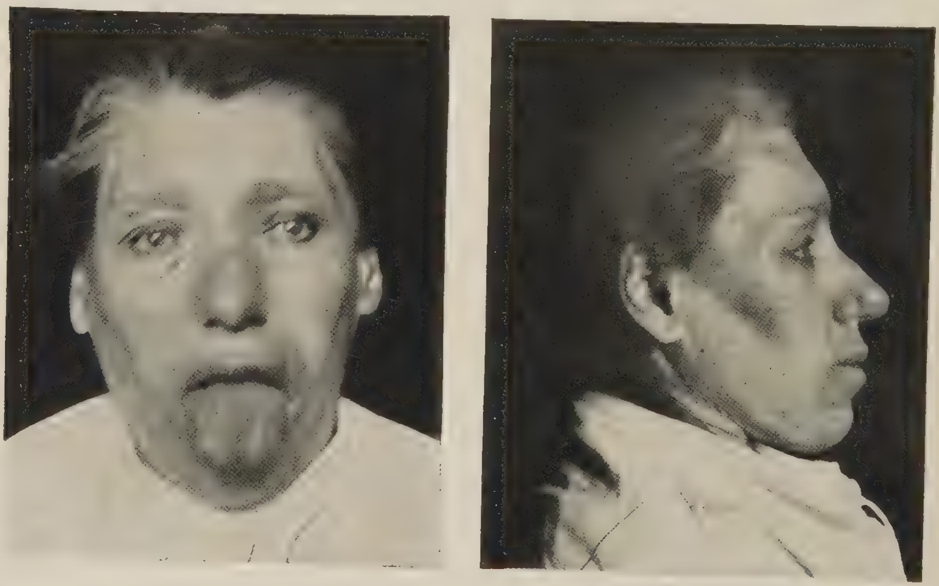

FIG. 48. FIG. 49.

Case of acromegaly (Observation XXXI).

Lately the patient has developed a pronounced cachexia. To this are added *slight signs of a myxedema*, especially a *cushion-like thickening* of the backs of the hands and of the skin of the supraclavicular fossæ. The pulse rate in the fever-free intervals (the patient now frequently suffers with bronchopneumonias) is about 70; the blood-pressure (*Gärtner*) lies near the figure 70; the former rather frequent diarrheas now occur only in single isolated attacks. There is mostly constipation. The circumference of the throat it is true has indeed increased, but a myxedematous thickening of the soft parts may indeed play a part in it.

The behavior of the thyroid gland in this case is instructive. We are dealing with typical case of acromegaly, which for a long time has shown signs of hyperthyroidism (sweats, tachycardia, tremor, slight exophthalmus, diarrhea, etc.). Later with the development of a cachexia, symptoms of hyperthyroidism retrogress more and more, to give place to a slight thyroid insufficiency.

The regressive changes in the thyroid gland that so frequently become established in the later stages of acromegaly might well be regarded as a partial phenomena of the degenerative alterations that in the later stages of acromegaly involve not only these organs that are the seat of the tendency to growth fostered by the acromegaly, but also the entire body as well. Hence in the later stages of acromegaly we may often see myxedematous symptoms, even in the absence of previous manifestations of hyperthyrosis. *Pineles* reports two cases of acromegaly with myxedema of the skin, stupidity, and weakness of memory. Improvement of the myxedema symptom followed the administration of thyroid gland, although they were not influenced by hypophysis tablets.

The pathologico-anatomical finding in the thyroid gland in acromegaly almost always shows something abnormal. When hyperthyrosis has existed, there is found the picture of a Basedow's struma. Otherwise there is seen almost always connective tissue proliferation, such as is found also in other organs in acromegaly, or colloid degeneration in combination with, eventually, high-grade sclerosing and atrophy of the parenchyma. *Gaussel* found a thyroid gland that was normal.

The *vascular system* in the later stages of acromegaly almost always shows changes. A slight grade of arteriosclerosis develops. Microscopical examination shows that the three vascular coats are involved in these changes, and that the media becomes poor in muscle fibers. The heart not infrequently hypertrophies, and the cardiac muscle soon degenerates. Especially those cases that are attended with other symptoms of Basedow's disease often show in the initial stages a slight degree of tachycardia; in all cases manifestations of insufficiency of the heart-muscle develop in the later stages. Varices are strikingly frequent.

In many cases the enlargement of the heart may very well be a partial manifestation of the true splanchnomegaly. *Humphry* describes a considerable cardiac hypertrophy without valvular changes in a man aged thirty-nine years. The case reported above (Observation XXIV) there was a broadening of the cardiac shadow, on X-ray examination, to 13 cm. The patient was thirty-two years old. Not rarely in addition to the enlargement of the heart there is found an enlargement of the liver, the spleen, the stomach, and the intestines. The enlargement of the liver is often only the sequel of an existing cardiac insufficiency, sometimes, however, the partial manifestation of a true splanchnomegaly. The enlargement of the spleen is a partial manifestation of the enlargement of the lymphatic apparatus to be described later. The dilatation of the stomach has been brought into association with the frequently observed polyphagia. *Cunningham* describes, in a case, a doubling of the length of the small intestines. Also the kidneys are often strikingly large, and in the urine a slight grade of albuminuria is not infrequently found. In two cases *Fischer* found enormous suprarenals, the enlargement affected especially the cortex; also *Delille* saw this several times. Lately *Fischer* and *Schultze* found enlargement of the suprarenals in two cases of acromegaly, in one of which (a case of early acromegaly) the suprarenals were enlarged about five times at least. Histological examination showed that the suprarenals in toto were enlarged quite uniformly. Also the kidneys were enlarged, showing on microscopical examination enormously large glomeruli.

In many cases *the pancreas* was found to be sclerosed, in other cases the pancreas was found to have been entirely normal (see later the combination of acromegaly and diabetes). In many cases of acromegalic gigantism the pancreas were of quite enormous size (up to 270 gm., *Launois* and *Roy*). A persistent thymus gland in acromegaly was already found by *Klebs* and *Fritsche*. Since their time this finding has been reported very frequently (*Dalton, Arnold* and *others*); detailed references as to the literature can be found in *Borchardt* (Deutsches Archiv für klin. Med.) *Pierre Marie* regards the enlargement of the thymus as a reviviscence. The enlarged thymus may produce a distinct dullness over the upper half of the sternum, although nothing should be concluded as to the enlargement of the thymus when this dullness is found, as in acromegalics the sternum is often thickened enormously.

The examination of the *blood* in acromegaly shows not rarely a reduction in the number of erythrocytes and in the hemoglobin contents. This was observed by *Sabrazès* and *Bonnes*. *Messedaglia* saw it in seven cases, *Rathy* in five cases. In the cases reported above, the case Str (Observation XXXI) had 4,700,000 red blood cells, 70 per cent. hemoglobin; the case Ta (Observation XXVII), 4,900,000 red cells and 82 per cent. hemoglobin; the case Ti (Observation XXV), 4,490,000 red cells and 95 per cent. hemoglobin; the case Bo (Observation XXVI) 5,210,000 red cells and 85 per cent. hemoglobin. Hence it seems that in the latter stages the erythrocyte count and hemoglobin contents are reduced.

The number of leucocytes is mostly normal (*Rothy*), although there is often found a somewhat reduced count. In my cases the case Ad (Observation XXVIII), showed 9800; case Bo (Observation XXVI) 8840; case Ta (Observation XXVII) 5600; case Un (Observation XXIV) 6240, and finally case Str (Observation XXXI) only 2900.

In the majority of cases the differential count shows a mononucleosis and not rarely an increase in the number of eosinophiles. *Sabrazès* and *Bonnes* found this in two cases, *Messedaglia* in seven cases (30–37.8 per cent. lymphocytes) *Rathy* in five cases; *Exner* in one case found 39 per cent. mononuclear cells and 61 per cent. eosinophiles. Likewise *Franchini* and *Giglioli* found mononucleosis in four cases, and among these hypereosinophilia in two cases. *Mendel* in one case found even 18 per cent. eosinophilia. Also *Messedaglia* and *Rathy* found for the most part an increase in the eosinophiles. In my own case Ta (Observation XXVII) showed 76 per cent. neutrophiles and 2 per cent. eosinophiles; case Da (Observation XXVIII) 74 per cent. neutrophiles and 6 per cent. eosinophiles; case Bo (Observation XXVI) 63.8 per cent. neutrophiles and 2.3 per cent. eosinophiles; case Ad (Observation XXIX) 66 per cent. neutrophiles and 1 per cent. eosinophiles; case Str (Observation XXXI) 60 per cent. neutrophiles; case Un (Observation XXIV) 57.6 per cent. neutrophiles and 1.3 per cent. eosinophiles and in case Ti (Observation XXV) 56.7 per cent. neutrophiles and 0.2 per cent. eosinophiles.

Lately a report on the blood-findings in three cases has been contributed by *Borchardt*. He found the erythrocytes approaching normal, the polymorphonuclear neutrophiles but little reduced, the eosinophiles mostly increased.

Hence the leucocyte count rather frequently shows, especially in the later stages, a relative and perhaps also an absolute reduction in the number of neutrophilic cells and a relative increase in the large mononuclears; perhaps this is the expression of a more or less well pronounced status lymphaticus, as has been found in several autopsies. (*Messedaglia*, *Schultze*, *Fischer*, *Rothy*, *Claude* and *Baudouin*, *et al.*).

The anomalies of *metabolism* in acromegaly need a very exact exposition. In many cases there exists obesity, as in the much-quoted case of *Strümpell*, although this was reported as simply "layer of fat abundant." Lately *Schultze* and *Fischer* have reported a case of *early acromegaly* who was fat. Also the patient in Observation XXIX was fat. In a review of the literature I have never found pronounced obesity. Frequently there exists voracious hunger and polyphagia, relatively rarely lasting for long periods, and for the greater part intermittent. Whether this symptom should always be regarded as a sign of hyperthyrosis, or whether it belongs to acromegaly proper, I shall leave unanswered.

Observations as to the *exchange of gases* in acromegaly have been carried out only by *Zantz-Geppert's* apparatus (*Magnus-Levy*, *H. Salomon*, and the recent investigations of *Bernstein* and *myself*). I have summarized these investigations as follows:

The investigations concerning the respiratory exchange of gases made up to the present do not appear to decide with complete certainty the question as to whether in acromegaly there occurs an increase in the caloric production that may be ascribed to the disease as such. In the case of *Magnus-Levy* the oxygen consumption and the production of carbonic acid doubtlessly are appreciably increased. But just here, according to the statement of the authors, there were present symptoms of hyperthyrosis that were not appreciable. In Case I of Salomon the exchange of gases is not appreciably heightened, in proportion to the size and body weight of the individual. The slight glycosuria can certainly not be regarded as a sign of increase (confer later on, in the chapter on the pancreas, the statements as to the exchange of gases in diabetes mellitus). Whether the sweats that occur in this case and the voracious hunger that occurred from time to time are to be referred to a hyperthyrosis is not at all certain in itself.

| Author | Sex and age | Height in cm. | Weight | $O_2$ need in c.c. per kg. per min. | $CO_2$ production in c.c. per kg. per min. | Remarks |
|---|---|---|---|---|---|---|
| Magnus-Levy.... | F 52 | 147 | 52 | 5.19 | 4.25 | No diabetes. |
| Salomon case 1... | M 49 | 183 | 112 | 4.9 | 4.33 | Sick for about 19 years, copious sweats, often voracious hunger and increased thirst. Potency not disturbed, built on herculean lines, diabetes (elimination of sugar reaches a few gm.). |
| Salomon case 2... | F 51 | 160 | 79.6 | 4.3 | 3.04 | The mother is also sick with acromegaly and diabetes. For 7 years alterations in face, for 3 years great thirst. Diabetes gravis, rather fat. |
| Salomon case 3.... | M 42 | 158 | 79.6 | 3.96 | 3.04 | Sick for about 20 years, no disturbance of potency. |
| Salomon case 4... | F 36 | 143 | 56.5 | 4.00 | 3.3 | Amenorrhea for 8 years, no diabetes. |
| Bernstein and Falta | M 31 | 175 | 89 | 3.55 | 2.73 | Strongly built, thyroid slightly enlarged, but no distinct signs of hyperthyrosis, alimentary glycosuria. |
| Bernstein and Falta | M 32 | 168 | 75 | 3.87 | 3.16 | Thyroid gland enlarged, slight signs of hyperthyrosis, no glycosuria on overloading. |

In case 2 the consumption of oxygen in proportion to the size of the patient is high. But there exists a severe diabetes. Also in case 3 the oxygen values lie somewhat above the upper limits of the normal. In case 4 the exchange seems to be normal. A heightening of the exchange of gases cannot be concluded from the cases reported by *Bernstein* and *myself*. On the whole the conclusion that *Magnus-Levy* and also *Salomon* have arrived at, namely, that in uncomplicated acromegaly the exchange of gases is not increased is correct. In the later stages of the cachexia and the decay, the exchange seems to be rather lower, especially when also the thyroid gland degenerates and myxedematous symptoms are added.

Up to the present only very few investigations have been made with regard to the *salt metabolism*. *Von Moraczewski* found in a case of acromegaly pronounced retention of phosphorus, calcium, magnesium, and chlorine (and also nitrogen), and explains this by the increased growth of the tissue.

*Investigations as to purin metabolism* have been instituted by *Nowaczinsky* and *me* in three cases. There were the cases already described as case T (Observation XXV), Un (Observation XXIV), and Ta (Observation XXVII). In case T (thirty-one years old) we found on purin-free diet a uric acid elimination between 0.72 gm. and 0.92 gm. in twenty-four hours. In case U (thirty-two years old) between 0.89 gm. and 1.16 gm.; fourteen days after the operation still higher values were found. As has already been mentioned, in this case the operation had no influence on the acromegaly. After the administration of sodium nucleinate there occurred a prompt increase of uric-acid elimination. In case Ta (thirty-three years) there were uric-acid values between 0.72 gm. and 1.29 gm.

Hence in all three cases were found values for the elimination of endogenous uric acid that reached the double or more than the double of the endogenous uric-acid factor observed in normal individuals. Any complications can hardly be regarded as the cause of this enormous increase. The patients were all free of fever; in case U there existed very slight symptoms of hyperthyrosis, which was however absent in both other cases. Ta had had lues, but now no symptoms of lues were present. Hence we must assume that the increase of uric-acid elimination in acromegaly occurs as such, the more so because in some cases of hypophysial dystrophia adipiso-genitalis we find strikingly low endogenous uric-acid values. In one case of acromegaly there occurred after the administration of purin-free material a prompt increase in the elimination of uric acid, while in the cases of hypophysial dystrophy the elimination of uric acid was extraordinarily reduced.

Such high values for the endogenous uric-acid elimination as we found in three cases of acromegaly have as yet been observed only in diseases in which lymphatic tissue goes to pieces in large amounts, or in certain febrile processes attended with marked hyperleucocytosis (acute articular rheumatism). In the cases of acromegaly the leucocyte counts were rather lower than normal. There was no ground whatever for the assumption of an increased melting down of lymphatic tissue. Further investigations as to this question are very desirable (see Chapter I).

Lately *Dr. Vias* has examined a quite chronically progressive case of acromegaly, and has observed no increase in the endogenous uric-acid elimination.

Quite *especially frequent* is acromegaly complicated with glycosuria or with *diabetes mellitus*. Already *Pierre Marie* had stated that in a third or a half of the cases of acromegaly glycosuria was found. Detailed references to the literature are to be found in the articles of *Launois*, and *Roy* and of *Borchardt*.

*Borchardt* collects 176 cases of acromegaly from the literature in which cases there exist specific statements as to the examination of the urine. In sixty-three cases, that is 35.5 per cent., diabetes was found; in eight cases alimentary glycosuria. In many cases the diabetes shows the ordinary course and eventually leads to death in coma. In many cases, however, as *v. Noorden* first emphasized, the glycosuria shows a striking independence from the sugar-value of the diet. The cases reported by me behaved thus:

| | |
|---|---|
| *Observation XXIV.*—U, on diet rich in carbohydrates | neg. |
| *XXV.*—T, alimentary glycosuria (100) | pos. |
| *XXVI.*—Bo, (distinct hyperthyrosis from thyroidin) | neg. |
| *XXVII.*—Ta, alimentary glycosuria also on diet remarkably rich in carbohydrates | strongly pos. |
| *XXVIII.*—Da, alimentary glycosuria | pos. |
| *XXIX.*—Ad, alimentary glycosuria | pos. |
| *XXX.*—St, alimentary glycosuria (also from levulose) | pos. |
| *XXXI.*—Str, at first alimentary glycosuria | pos. |
| then later, on many investigations | neg. |

Among eight cases, five were distinctly positive, and one for a time weakly positive. In one case (Ta) we may even speak of a very light diabetes.

The behavior toward adrenalin was tested in two cases (Observation St and Observation Ta) with negative results.

In many cases alimentary glycosuria or diabetes occurs only in the initial stages of acromegaly; later these cases show a marked tolerance. *W. Schlesinger* and *Borchardt* each report such a case. Lately also *Cushing* has reported about such cases. In the case of *Borchardt* the diabetes had existed five years; and later there occurred no glycosuria on the injection of 150 gm. of grape-sugar. It should be mentioned that not rarely such diabetic disturbances of metabolism occur in Basedow's disease (thyrogenic glycosuria).

In the few cases in which I examined the excitability of the *vegetative nerves* showed a very diverse behavior. In the case Ta there occurred, after the injection of adrenalin, marked rise of blood-pressure, tachycardia and arrhythmia. There also occurred marked diuresis, but not glycosuria. As in this case sugar appeared in the urine after overloading with carbohydrates, it stands as a fine example of the independence of the alimentary and the nervous factors (*Falta, Newburgh,* and *Nobel, Case* 43). Also the injection of pituitrinum infundibulare acted as a marked diuretic. After the injection of pilocarpine there occurred only moderate sweats and a moderate flow of saliva; although the patient stated that she suffered with crises of copious sweats. In other cases the action of pilocarpine on the excitability of the sweat glands was more distinct. Hence there may occur temporary conditions of marked irritability of the sweat glands, without hyperexcitability of them existing during the interval. The outbreaks of sweat are known to be a very common symptom of acromegaly. *Magnus-Levy* and *Salomon* in their cases of acromegaly regard the sweats as the symptom of hyperthyrosis; however, it seems to me certain that the outbreaks depend on another cause lying in the nature of acromegaly itself, as we see them also in the cases in which other symptoms of Basedow's disease—before all, the cardinal symptom of the hyperthyrosis—the tachycardia are absent. This was the case, for instance, in case Ti (Observation XXV).

The polyuria may also be looked upon as dependent on an abnormal condition of excitability of the vegetative nerves. This also usually occurs only temporarily in crises. The specific gravity of the urine may sink in these attacks to very low values, reminding us of a true diabetes insipidus. As I have mentioned before, there may exist in many cases an especial sensitivity of the nerves of the kidney for adrenalin or for pituitrinum infundibulare. It is not clear how far such changes in the condition of excitability of certain vegetative nerves may be brought into relationship with functional alteration of the hypophysis. At most we may conjecture that the critic polyuria may be associated with temporary irritation of the posterior lobe and with the increased production of hypophysial "diuretin."

That complication with hyperthyrosis or hypothyrosis influences the condition of excitability of the vegetative nerves in many ways needs no further consideration in detail.

Very often the pathologico-anatomical examination in advanced cases, shows proliferation of the connective-tissue elements in the vegetative nerves and ganglia (*Marie* and *Marinescu*).

The symptoms on the part of the *somatic nervous system* are very manifold. To the early symptoms often belong the very burdensome rheumatoid pains and eventually acroparesthesias (*Sternberg*). In many cases the pains occur during night, so that the patient must get up and walk around the room (Observation XXIV). Also sensation of heat in the fingers may occur. In one case there occurred transitory swelling of the finger-joints simultaneously with the pains. Whether combinations with continued articular swellings and chronic deforming processes in the joints, as was present in Str, Observation XXXI, are common, I have not been able to glean from the literature. The behavior of the reflexes varies. Sometimes they are increased, sometimes reduced.

Also alterations of the mind and intelligence occur in acromegaly. In many cases there exists a characteristic apathy, a want of initiative, and a slowing of the speech. In rare cases, conditions of exaltation are observed. The pathologico-anatomical examination of the nervous system shows no constant findings; except that in the later stages there occurs regularly an increase of the connective-tissue elements in the nerves.

Among the symptoms of acromegaly there is still a group that has nothing to do with the disease process in itself but is produced mechanically by the *enlargement of the hypophysis*. To these belong first of all the changes in the sella turcica; *Oppenheim* was the first to recognize enlargement of the sella during life by means of the X-rays. Since that time X-ray technique has improved wonderfully and has become of important diagnostic aid. The changes in the sella may be very different; frequently when the tumor is situated purely intrasellarly there exists a widening out of the sella with deepening of the floor. This may bring the bony partition between sella and sphenoidal sinuses to paper-like thinness or to actual perforation; even when the tumors are large the clinoid processes may remain intact. In very large tumors too, however, there may be a widening of the entrance to the sella and final destruction of the clinoid processes. The tumor may also calcify. Calcifications of the dura are not rare.

The following X-ray finding in a typical case of acromegaly serves as an example:

*Observation XXXII.*—U, Dec. 9. The sella turcica is not only widened on the whole to twice its size (measured in the sagittal direction) but also is very roomy at its introitus. This also is at least double as wide as normal. The floor of the sella turcica has its homogeneous rotundity infringed upon, and is polygonal with washed-out borders. Several crumbly calcareous masses in the interior of the sella may well be supposed to be calcified tumor-masses. The widening that is here present shows itself in a sharpening at its base.

The lack of an enlargement of the sella does not militate against acromegaly. On the one hand as we shall see later there may be present specific microscopical alterations also in hypophyses that are scarcely enlarged, especially in the initial stages of the disease; and on the other hand there may be present a tumor of the hypophysis in the sphenoidal sinuses proceeding from epithelial rests of the hypophysial duct, or such a tumor of the hypophysis of the pharyngeal vault. In the first case the floor of the sella may be even eroded from below, and thus the connection with the hypophysis be established secondarily (*Erdheim*).

Later, in the consideration of the tumors of hypophysis, we shall come back to the subject of the differential diagnostic significance of the alterations of the sella.

To the symptoms called into existence by the pressure of the growing tumor belong also headache, and eventually dizziness and vomiting. But the last two symptoms as well as paresis of the cranial nerves are in this disease relatively rare.

On the contrary there are found more frequently disturbances on the part of the *optic nerves*, disturbances not rarely in the form of bitemporal hemianopsia and hemianopic pupillary reaction; the latter according to researches of *Wernicke* and *Déjerine* almost surely indicate a hypophysial tumor.

In addition to the hemianopsia there is found, also commonly, simple amblyopia; these manifestations may occur unilaterally. They can lead to blindness of one or both eyes; examination of the eye-grounds shows for the most part alterations of the papillæ in the sense of a neuritis (in 40 per cent.)

or of an atrophy, rarely choked disc. I shall return to the manifestations of brain-pressure in the consideration of the subject of nonacromegalic hypophysial tumors.

## Pathological Anatomy of the Hypophysis

I now turn to the treatment of the *nature of the hypophysial tumors in acromegaly*. Although it is the most important, I have placed it at the end of the long series of symptoms, because it acts as transition to the subject of the pathogenesis of the disease. To-day we may state with rather great probability that in every typical case of acromegaly there exist in the anterior lobe of the hypophysis *adenomata* or *adenocarcinomata*, which in rare cases are dystopic, proceeding from cut-off hypophysial cells. The questions on this subject that have been energetically discussed during the last decade are: Are there cases of acromegaly without hypophysial tumor, or without the adenomatous changes in the hypophysis regarded as specific; and, are there cases of such tumors that do not show any of the symptoms of acromegaly? These questions have recently been discussed with temperament in a monograph by *B. Fischer;* I shall refer the reader to the literature on the subject and shall attempt here only to bring to the front the principal opinions on this subject.

*Hanau* first pointed out that in the overwhelming majority of cases of acromegaly, adenoma of the hypophysis was observed. Through the discovering of a specific coloration for the cell granules in the chromophilic cells by *Benda* the recognition of the adenomatous tumors has become essentially easier. *Benda* himself found in three of four cases of acromegaly the cell granules in monstrous excess in the adenomatously degenerated anterior lobe of the hypophysis. For most part the forms of adenoma are benign; the cells in the malignant form, in which growth is very rapid, may remain very small. In such cases under circumstances the presence of these among the gland-cells can be determined only by the use of *Benda's* stain. Such malignant adenomata were for the most part formerly regarded as carcinomata. *Fischer* says that the other kinds of tumors, such as carcinomata, sarcomata, endotheliomata, etc., never produce acromegaly; this statement seems to be correct except that the position of the cases of typical acromegaly in which the pathological finding points to adenocarcinoma. I refer to the case of *Cagnetto*. *Cagnetto* described a large adenocarcinoma with abundant secretion granules, proceeding from the glandular part of the hypophysis, which led to metastases in the spinal cord; in these metastases the chromophilic cells were demonstrable likewise. Fig. 50, for which I am indebted to *Prof. Stoerck* shows a similar case. Here again there exists a noticeable analogy to the thyroid gland, in which adenocarcinomata associated with metastases and manifestations of Basedow's disease are described. If in such cases moreover with malignant degeneration of the adenomata the chromophilic cells are sometimes very few, this would not militate against the applicability of the above-mentioned postulate, as in malignant tumor there frequently sets in an anaplasia of the cells, as *Fischer* correctly points out. Again cases of acromegaly have been described, in which the sections indeed disclosed tumors proceeding from the glandular part of the hypophysis, which tumors, however, were cystically degenerated, and showed but very little glandular tissue. Here it is indeed remarkable how rapidly after extirpation of the part of the tumor, in the cases thus far operated on, the manifestations of acromegaly ameliorate. These cases, however, are fresh ones; in very old cases with acromegaly they perhaps would not ameliorate so rapidly. Finally the cases with colloid struma of the hypophysis have been brought as evidence against the postulate, in that in acromegaly such strumas may be found without proper adenomatous formation, and on the other hand there may be found typical strumas with small adenomata without acromegaly. As example of the first type I mention the case of *Widal*, *Roy*, and *Froin*. Here there existed typical acromegaly in a sixty-six-year-old man, and atrophy and sclerosis of the gland substance which was permeated with colloid cysts; in spite of the atrophy there could be found rather numerous chromophilic cells. As example of the second type I refer to the cases of *Zack* and *Cagnetto*. The case of *Cagnetto* was that of a thirty-two-year-old woman without acromegaly; the hypophysis weighed 1.55 gm. which is thrice the normal weight; microscopically was found a

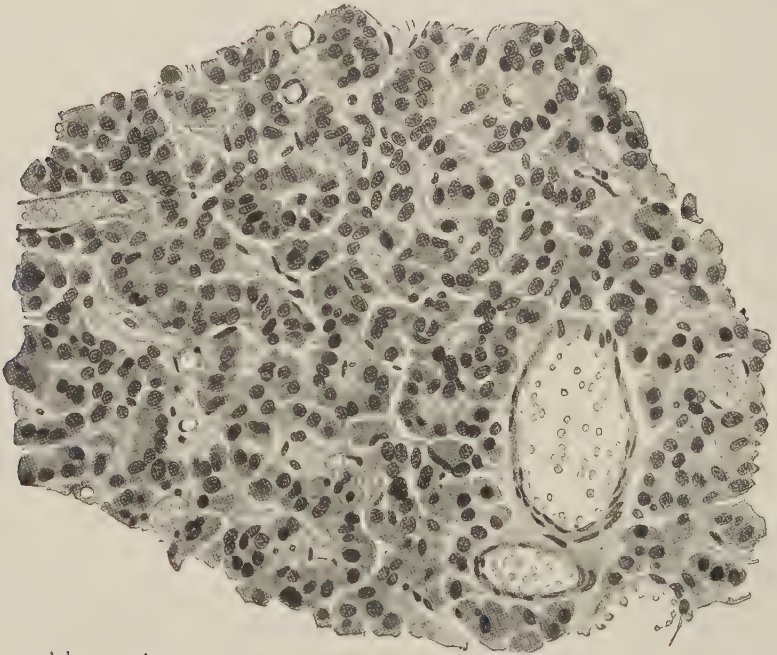

FIG. 50.—Adenocarcinoma of the hypophysis made up, in great part, of eosinophilic cells.

typical struma, in which small adenomatous portions alternated with strumous portions. The analogous relation with the thyroid furnishes a key in this case. There are also cases of Basedow's disease in which only "Basedow's islands" are to be found in the thyroids.

**Pathogenesis.**—Already *Pierre Marie* had recognized the connection of acromegaly with the hypophysis; at all events he supposed that the tumor destroyed the functionating pituitary tissue. *v. Strümpell*, *Arnold* and *others* advocated the opinion that enlargement of the hypophysis was coordinated with that of the acral parts, in other words that it is only a partial phenomenon of a general disturbance of metabolism (endogenous theory). The theory of hyperfunction was first upheld by *Tamburini*, *Benda*, and *Massalongo*. Other authors have supposed a primary disturbance of function of the sexual glands (*Freund*, *Verstraeten*, *Stumme*, lately *E. Mayer*, especially).

Finally the endogenous theory has been modified by other authors (*Claude*, *Delille*) in that they regard acromegaly as a pluriglandular affection.

The assumption of a loss of function of the hypophysis in acromegaly can at the present day no longer be regarded as correct, we shall see later that processes that destroy the glandular hypophysis never lead to acromegalic symptoms, but to symptoms of an entirely different kind. The same thing occurs in animals after the hypophysis has been extirpated. The supposition of a primary functional disturbance of the sexual glands is no longer tenable, in that, as we shall see later, there are cases of acromegaly in which the sexual glands still functionate, even although the disease has been fully developed after several years. Against the endogenous theory, speaks, among other facts, the results of the partial extirpation of the tumor of the hypophysis, as will be dealt with more in detail later. This places the hypophysis entirely in the middle-point of the pathogenesis of acromegaly. That in acromegaly *other ductless glands are involved* very frequently was already mentioned by *Pineles*, which fact, as we have seen, makes the disease picture very manifold. The circumstance that this involvement is a very diverse one, that, for example, at one time there occurs on the part of the thyroid symptoms of hyperfunction and at another time symptoms of those of insufficiency shows once more the predominating position of the hypophysis. Hence only those manifestations may be regarded as cardinal symptoms of acromegaly, which are to be referred directly to the alteration of the hypophysis; there are in addition to these a herd of the secondary symptoms.

Besides the results of the surgical treatment it is especially the similarity of the pathologico-anatomical findings in the hypophysis in acromegaly with those of the thyroid in Basedow's disease that indicate *that acromegaly is brought about through an increase in the function of the glandular hypophysis.*

Against this assumption there has been objected that in many cases as above mentioned, there are found strumas of the glandular hypophysis in which degenerative manifestations predominate, and that on the other hand the strumas or small adenomata occur without acromegaly. I believe that the dictum of *Kocher* that there are strumas and strumas holds for the hypophysis as well as for the thyroid. To-day no one would be surprised that, especially in the old Basedow's cases, parts of the thyroid are degenerated, and that on the other hand small adenomata of the thyroid gland are often unattended with any of the manifestations of Basedow's disease. The morphological finding does not always indicate the functional condition. Finally should be mentioned that in rare cases of acromegaly entirely normal hypophyses were found. In many of these cases the diagnosis of acromegaly is doubtful (syringomyelia, congenital abnormal size of the acra, etc.[1]) In other cases we find dystopic adenoma of the hypophysis which proceed from cut-off cells [versprengte Keime] (*Erdheim* and *Haberfeld*).

I have already referred several times to the manifold analogies that exist between the lesion of the thyroid gland and those of the hypophysis. As we shall see later the assumption that hypophysial dystrophia adiposogenitalis depends on a lessened function of the hypophysis is based on experimental pathology in a fashion analogous to that in which the assumption of myxedema is a hypothyrosis has been demonstrated by experiment. On the contrary the conditions for acromegaly are to-day very much more unfavorable than those for Basedow's disease. The most important support for the theory that it depends on a hyperfunction of the hypophysis lies, as I have mentioned previously, in the results of the surgical treatment of acromegaly. Reduction in the size of the hypophysis through extirpation of portion of the gland leads in many cases to a retrogression of the acromegalic manifestations. That this is not true in all cases, for example, in the case of U (Observation XXIV), does not seem to me of great significance, as on account of the slight visibility of the field of operation, we do not know anything as to the size and value of the piece of tumor left behind. In analogy with experiences in Basedow's disease it is very probable that a result could have been obtained by a further reduction of the tumor.

On the contrary, the attempts to produce a hyperfunction of the hypophysis experiments have hitherto been attended with very slight results. The stimulating [fördernd] influence of the hypophysis on the growth as inferred from the clinical observations, has as yet not been demonstrated experimentally with certainty. The attempt on feeding of growing animals with hypophysis substance seems to me not to have furnished convincing results as yet. Worthy of note in this regard are the statements of *Exner* that implantation of several hypophyses hastened the growth of young rats.

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[1] Also tall eunuchoids have been confused with acromegalics. This for instance we find described by *Gallais* a case of "gigantisme acromegalique sans élargissement de la selle turcique" with "inversion sexuelle and feminisme mental." In this case quite sudden rapid growth started at fourteen and one-half years of age, that was also present to lesser degree in the twenty-fifth year. Hands and feet were very long and slender. In the illustration that accompanies the report of the case absolutely nothing of acromegaly is to be seen. It shows however typical eunuchoid obesity.

The investigations with injection of pituitary extracts have indeed led to recognition that the latter possess not inappreciable physiological actions, but, nevertheless, we have not been able to bring them into relation with the pathogenesis of acromegaly with such certainty as is the case in analogous experiments in Basedow's disease. It is to be regarded as established, however, that the physiological actions of the extracts from the anterior lobe are quite other than those of extracts of the pars intermedia and posterior lobe. Let us first consider the action of the latter.

The *extract from the pars intermedia and posterior lobe*, that has been made entirely free of albumin, has in many respects actions similar to adrenalin, without however giving the color reactions of adrenalin. The extract from the entire hypophysis acts as a blood-pressure raising agent and a pulse-slowing agent by contraction of the peripheral vessels (*Oliver* and *Schäfer*). *Howell* later found that this action is due solely to the extract of the infundibular part. The initial lowering of blood-pressure that is sometimes observed, may be referred to the admixture with other substances, perhaps with those which are identical with what are found in large amounts in the glandular extract. These can be separated from the other by extraction with alcohol. The blood-raising action of pituitrinum infundibulare distinguishes from that of adrenalin in that it often remains absent on short spaced repetition of the injections. The vasoconstrictor action can, in man, be very readily shown. After subcutaneous injection of 1 to 2 cc. we mostly find a distinctly pronounced local ischemia that often lasts longer than an hour. Subcutaneous injection of so small an amount raises the blood-pressure, in man, for a long time after the injection. Also it produces mydriasis of the isolated ball of a frog's eye. Further it acts as a strong diuretic (*Magnus* and *Schäfer*) by a dilatation of the renal vessels (*Haliburton*); according to *Pál* only the peripheral section of the renal artery dilates, while the proximal part contracts. The different vascular distributions behave especially diversely to the action of the drug. The diuresis may be, in man, very considerable; in case Ta, Observation XXVII, we saw an increase in the amount of twenty-four-hour urine from 800 cc. to 1200 cc. According to *Kepinow* pituitrinum infundibulare sensitizes the points of attack of adrenalin. The actions of pituitrinum infundibulare thus far detailed have, with the exception of the slowing of the pulse, all adjusted to the irritation of the sympathetic nerves. It also acts, however, on certain organs supplied by autonomous nerves in the sense of a stimulation through the autonomous nerves. While according to *Frankl-Hochwart* and *Fröhlich* the autonomous vagal cardiac, the nerve of the pancreas, the chorda tympani, and the nerve erigentes are not influenced as to their excitability, the excitability of the nerves of the urinary bladder and the musculature of the uterus are markedly heightened, or the uterine musculature is brought to strong contraction. This action, according to the experiments of *Fleming* and *myself* may be set aside through the use of atropine. It is only constant in the gravid uterus, while in the virginal uterus there may even occur inhibition of the peristaltic waves. Also certain chemotactic actions (mononucleosis, hypereosinophilia) are perhaps to be referred to the irritation of autonomous nerves. According to *Ott* and *Scott*, and *Schäfer* and *Mackenzie*, the extract of the posterior lobe contains galactogogue substances.

Also the actions on the metabolism are very appreciable. *Schiff* saw after feeding a case of acromegaly with hypophysis tablets a 16 per cent. increase of elimination of phosphorus, in a case of paralysis a 25 per cent. increase. The increase principally affected the elimination through the feces. According to our investigations (*Bolaffio* and *Tedesco*) this action is to be referred to the pituitrinum infundibulare, as we saw appreciable increase in the elimination of phosphorus after its injection. That a large part of the phosphorus in eliminated through the feces finds its explanation in the fact that also the calcium elimination through the feces is much increased, and the calcium travels with the phosphorus in the intestine. We also found an appreciable increase in elimination of nitrogen in fasting dogs and in those in whom the nitrogen metabolism was in equilibrium. In a case of acromegaly to whom he administered hypophysis tablets, *v. Moraczewski* found an increase in the elimination of nitrogen, but not in that of calcium.

*Cushing* recently states that, according to his investigations, extracts from the posterior lobe of the hypophysis or from the pars intermedia, also possess an action on carbohydrate metabolism. Intravenous injection of posterior lobe extracts into a rabbit always produces glycosuria. Further subcutaneous or intravenous injection of extract of posterior lobes should reduce the tolerance limits for carbohydrates also in animals with heightened tolerance limits in which the hypophysis had been removed. *Bernstein* and *I* could not corroborate *Cushing's* statement in experiments that we instituted, using the otherwise active pituitrin of *Parke, Davis & Co.* First, on the injection of large quantities (up to 33 cc.) to rabbits and dogs, we never saw the appearance of glycosuria. Nor, according to earlier experiments of *Priestley* and *myself* is there an increase in the blood sugar-contents. Second, in experiments on man we have never been able to influence [by its use] the tolerance limits for carbohydrates. After the injection of pituitrinum infundibulare (up to 3 cc.) we never saw the occurrence of alimentary glycosuria on the administration of 100 gm. dextrose, and in individuals who already had alimentary glycosuria, this was never increased under the influence of pituitrinum infundibulare. Nor did we see an increase in the elimination of sugar in diabetics. Especially important seem to me the experiments on diabetics who at the time were sugar-free. Here if the tolerance limits for sugar were reduced as a result of the injection, we would expect to see a recurrence of the sugar. Finally in respiratory experiments on men there occurred regularly after the injection of pituitrinum, an increase in the production of carbonic acid or of consumption of oxygen, but never a distinct rise of the respiratory quotient.

As example I cite the following experiment: Case Ti (Acromegaly)

| Date | $CO_2$ | $O_2$ | RQ |
|---|---|---|---|
| February 14 | 257.5 | 342.0 | 0.753 |
| February 16 | 247.7 | 329.8 | 0.748 |
| 40 min. after the injection of 2 cc. pit. inf. | 297.0 | 393.9 | 0.754 |

Also if the investigation was made a short or a long time after the injection, there could never be observed a distinct rise of the respiratory quotients. The increase in the respiratory metabolism that we found after the injection of pituitrinum infundibulare may very well be referred to an increased stimulation of smooth-muscled organs probably also of an increased activity of the liver. At least the hyperemia of the liver that *E. Neubauer* found in oncometric experiments seems to point that way.

Also *Miller* and *Dean Lewis* state that intravenous or intraperitoneal injections of extracts of posterior (and anterior) lobes of the hypophysis in dogs indeed may sometimes induce transitory, very weak glycosuria; it is here very questionable, however, whether this has anything to do with the internal secretion of the hypophysis.

The extract of the *glandular* portion of the hypophysis was formerly designated as entirely without action. *Ivković* and *I* found, however, that one of the extracts furnished to us for trial by the firm of *Parke, Davis & Co.* possessed a pronounced depressor action; after the intravenous injection of 2 to 3 cc. of this extract there occurred a depression of the blood-pressure, which latterly again returned spontaneously to the normal; previous administration of atropine would not hasten this return to normal, but on the contrary would retard it. When large doses of the extracts were used, in two of our experiments the blood-pressure sank to zero, and there was cessation of respiratory and cardiac action; in one of these experiments the heart could be made to beat again by administration of pituitrinum infundibulare; the blood-pressure gradually rose to normal again, and the animal entirely recovered. Later *Hamburger* without knowing about our experiments, likewise reported concerning the depressor action of the extract of the glandular hypophysis. In numerous experiments that *Bernstein* and *I* made on human beings since that time we could never demonstrate a distinct sinking of blood-pressure after the subcutaneous or intravenous injection of several cubic centimeters of this extract. Hence the dog seems very much more sensitive in this direction. We did observe in human beings, however, an extremely striking action. Shortly after the injection of a slight amount of the extract—often 2 cc. intramuscularly was sufficient—the production of $CO_2$ and the consumption of oxygen were reduced. At the same time the respiratory quotient rose appreciably. This rise in the respiratory quotient lasts in man for thirty to forty-five minutes, then it gradually sinks to the normal, while ordinarily the lowering of the total respiratory exchange of gases lasts much longer.

I cite the following experiment as an example: Case Ti (Acromegaly)

| Date | $CO_2$ | $O_2$ | RQ |
|---|---|---|---|
| February 23 | 256.1 | 327.9 | 0.780 |
| One-half hour after intravascular injection of pit. gl. | 230.77 | 246.96 | 0.935 |

In experiments on a dog we found that on much longer doses (up to 30 cc.) the lowering of the respiratory exchange of gases was much the less distinctly pronounced, and that the rise in the respiratory quotient also was not so well expressed as in man.

The extract used is albumin-free, but often gives a biuret reaction. The slight amounts of albumoses present could not cause the depressor actions that we observed, as the action occurred just as promptly after the albumoses were removed. Also the chloretone employed with the extract furnished to us could not account for this action. Finally it could be shown that the active principle is not cholin, as the depressor action on the blood-pressure continued to exist after the previous administration of atropine.

The interpretation of these results is attended with great difficulties. The circumstance that we were not able to observe a depressor action in man does not signify very much. It is possible that also here a dilatation of the vessels occurs, but the action of this on the blood-pressure is neutralized by counter-regulations. The depressor action on the exchange of gases would let it be supposed that temporarily the tonus of organs with smooth musculature or that the activity of the great glands of the body is reduced.[1] Still harder to explain is the action on the respiratory quotient. We originally thought that the extract called for a mobilizing or increased combustion of the carbohydrates, and that on account of this there occurred also a reduction in the total combustion. But in experiments on two severe diabetics it was shown that here also there occurred a lowering of the respiratory metabolism, but that here the respiratory quotient remained quite unaffected. The experiments also speak against the near-lying objection that the rise in the respiratory quotients has its foundation in an alteration in mechanism of breathing. Further it was shown in numerous experiments that were constantly modified, that this extract does not act as a glycosuretic, and does not essentially influence an existing alimentary glycosuria. Exceptions perhaps are certain experiments on diabetics on whom after institution on a very low elimination of sugar, there several times occurred a slight increase in the glycosuria after injection. Finally, however, it was shown that after the injection of this extract there was never observed either in experiments on man or on dogs, an increase of the blood sugar contents, but on the contrary the figures representing this sank. *Borchardt* saw the occurrence of glycosuria after the injection of hypophysis extract in the rabbit. In dogs for the most part this was wanting. According to our experiment I would not estimate very highly the value of the evidence of the experiments on the rabbit. After all that I have said thus far as to the action of the extract of the glandular part of the hypophysis, it may well be assumed that the latter in some manner involves the carbohydrate metabolism, not, however, by mobilizing carbohydrates in the liver. Hence there remains scarcely more than the assumption that it increases the combustion of the sugar in the periphery. With this agrees very well the decrease is the blood sugar. I am fully aware, however, that this is nothing more than a hypothesis.

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[1] *E. Neubauer* was so kind as to make a oncometric experiment on the liver of rabbits. He found after injection of pituitrinum glandulare distinct reduction of the liver volume.

If we consider once more the individual physiological actions that have thus far been demonstrated for the glandular or the infundibular extract of the hypothesis, we readily see that very little for the pathogenesis of acromegaly can be got out of it. The function of the cardiovascular apparatus is ordinarily not altered in acromegaly in a striking manner, in so far as manifestations of hyperthyrosis or hypothyrosis are not present at the same time.

Closest lies the idea that the polyuria sometimes observed may be referred to a temporary irritation of the posterior lobe through the growing adenoma of the anterior lobe. It lies within the confines of this conception that such polyurias also frequently occur in tumors of the hypophysis of other sorts, that are associated not with phenomena of hyperfunction of the hypophysis but on the contrary with those of insufficiency (see later). As far as the genital disturbances in acromegaly are concerned, the described action of the infundibular extract on the genital organs has not as yet helped to make them more intelligible. In acromegaly we find, as has been stated in detail before, rather an increased activity of the interstitial glands, and eventually, after transitory increase of function, setting aside of the functions of the sexual glands. In hypophysial dystrophy there exists a severe dystrophy of the genital organs that includes also the interstitial glands. It is therefore very much more likely that these alterations of the genital function rather stand in correlation with alterations in the function of the *glandular* hypophysis. Nothing at all is thus far known, however, as to the action of the glandular extract on the sexual glands. The respiratory exchange of gases does not tend to become altered in acromegaly, at least as far as there exist no complications with hyperthyrosis, and in dystrophia adiposo-genitalis it is, as we shall see later, perhaps sometimes reduced. The depressor action of the glandular extract and the furthering action of the infundibular extract can hardly be called upon to explain this disease picture. Also the explanation of the disturbance of carbohydrate metabolism so commonly observed in acromegaly seems to me to encounter unsurmountable obstacles.

*Rath* and later *Loeb* supposed that in acromegaly the tumor of the hypophysis pressed on a neighboring sugar center; the diabetes in acromegaly would thus be placed in analogy to the glycosuria sometimes occurring in apoplexy. This view has recently been adopted by *Aschner*. This author succeeded in demonstrating that a sympathetic center lies in the subthalmic region, the irritation of which causes glycosuria. The glycosuria does not occur after transection of the splanchnic nerves and therefore like that of *Claude-Bernard's* piqûre goes over the chromaffin tissue. In spite of the convincing experiment of *Aschner*, I cannot agree with his conclusion; it is not clear to me why just in acromegaly, a developing hypophysis tumor should press on this center, while the tumors of the hypophysis without acromegaly, that often lie in the hypophysial duct or even extrasellary, and that give occasion to symptoms of great brain pressure, produce no diabetes; in these cases, on the contrary, we shall see later, the tolerance limits for carbohydrates are practically always appreciably raised.

*Pineles* supposes a correlative affection of the pancreas. Actually *Hansemann* and *Dallemagne* have found atrophy of the pancreas in acromegalic diabetes. It is indeed very probable that in the cases of acromegaly combined with severe diabetes the pancreatic genesis stands in the foreground. We see in acromegaly degenerative changes in almost all the organs occur simultaneously with or in the course of the period of increased tendency for growth, and the insular apparatus may rapidly become involved in the process just as are involved the sensitive glands of generation.

*Schlesinger* assumes in acromegaly not only the occurrence of a true pancreatic diabetes but also of a brain-tumor diabetes. *Lorand* is of the opinion that the glycosuria of acromegaly is thyrogenic as a result of the relationship of the hypophysis to the thyroid gland. The views may be very well true for a part of the cases, namely, that part in which distinct manifestations of the hyperthyrosis are present. How shall we explain, however, the inclination of alimentary glycosuria or even a spontaneous glycosuria in these cases in which, as in case Ti (Observation XXV) the hyperthyrosis is entirely absent, quite apart from the cases with severe diabetes or diabetes leading to coma? *Naunyn* and later *Borchardt* regard the diabetes in acromegaly as directly hypophysial, that is, brought about through the production of an agent that induces glycosuria. The view seems to me to have a certain support in the repeatedly mentioned investigations of *Bernstein* and *myself*. I have previously stated in detail that the glandular extract somehow seems to enter in the regulation of the carbohydrate metabolism, but I am not in the position to say anything exact about this action. We are thus evidently guided by opinions, and I would like to be understood as believing that in the majority of cases a premature degeneration of the insular apparatus seems the most likely explanation.

Pathological physiology has as yet furnished with very little for the understanding of the pathogenesis of acromegaly. As yet just the most important symptoms, the increased tendency for growth of a certain part of the organism, especially the osseous systems, have not been reproduced experimentally. In spite of this the supposition of a hyperfunction of the hypophysis in acromegaly is to-day the only satisfactory one.

For this assumption speaks:

1. The opposition of the clinical pictures of acromegaly and hypophysial dystrophy.
2. The fact that the latter may be produced by extirpation of the hypophysis.
3. The results of surgical interference.
4. The analogy with affections of the thyroid gland.

**Early Acromegaly.**—The statements thus far set forth as to the pathogenesis of acromegaly are concerned with the clinical picture that we meet within adults. Acromegaly indeed develops almost exclusively after the twentieth year. We must now consider the important question as to whether there exists an acromegaly of child or adolescent life, and whether the picture of early acromegaly deviates from that of adults. *Brissaud*, and *Launois* and *Roy* adopt the view that hyperfunction of a hypophysis in early youth before the closure of the epiphysial juncture leads to gigantism and after the definite ending of growth to acromegaly. According to this view all pathological gigantism would then be acromegaly. This view was already vigorously opposed by *Pierre Marie*. I shall deal with this question later in the chapter on gigantism, and only would remark here, that I also cannot subscribe to this view, as may be plainly seen on the perusal of the following details. I believe much more that there exists an early acromegaly with gigantism; only it seems that this condition is relatively very rare, and is much more manifold as to its symptomatology than is the typical acromegaly of adults.

It here seems to me necessary to enter more in detail concerning the reports on this subject that occur in the literature. Most intelligible is a group of cases in which the clinical picture is very similar to the acromegaly of adults. To this group belong the case described by *Arnold* as early as 1891. According to the definite statement of the author the acromegalic manifestations in this patient began to develop distinctly in the eighteenth year of life. In a brother of the patient, who also suffered from acromegaly, the beginning of the affection came on at a still earlier period of life. There is no doubt at all that this case was one of acromegaly; this was shown by the typical thickening of the bones that increased in intensity toward the periphery. Also the exact microscopical examination of the bones showed architecture typical for acromegaly. In the muscles, in the peripheral nerves, the vessels, and the weak parts, there may everywhere be found hyperplasia of the connective tissue. It is worthy of note in this case that the sella turcica was not essentially widened, and that further there was a markedly developed hairiness, especially of the extremities. Hence although in this case the beginning of the affection occurred at the time at which normally the epiphyses are not as yet closed, increase in height was not present in this case. In this respect it seems to me significant that there were not eunuchoid manifestations in this case; on the contrary, as was evinced by the hairiness, rather was there an accentuation of the function of the interstitial glands.

A case of *Claude's* shows that in acromegaly the closure of the epiphysial junctures may occur prematurely. It was that of a girl nineteen years old in whom the acromegalic manifestations had gradually developed since the fifteenth year. The epiphysial junctures were completely closed, and there was no tendency to abnormal height.

Very important is the case recently reported by *Schultze* and *Fischer*. Here the disease began at the eleventh year of life. Since that time had existed headache, vomitings, and temporary salivations. The patient had never menstruated. In the course of three days she became blind and almost deaf (probably on account of narrowing of the inner ear on account of osseous thickening).

The girl was 167 cm. tall, weighed 81.5 kg. At various places there were pronounced pigmentations, the skin of the entire body was rather dark, from the navel there was marked development of the hair in the middle line, also hair on the upper lip. At various places dark nevi. Inclination for sweats. Head very long, horizontal circumference 59 cm. Upper lip markedly cushioned, nose thick. Tongue enormously thickened, alimentary glycosuria negative. Bilateral choked disc and atrophy. Death manifestly due to cerebral pressure. Pronounced obesity. Thymus hyperplastic. General splanchnomegaly. Also the liver, kidneys, and especially the suprarenal glands greatly enlarged (the last to five times their size). Uterus small, infantile cysts of the ovaries, no formation of follicles. The tumor of the hypophysis was of abnormal size (6.5 to 4.5 cm.). Microscopically typical adenoma rich in cells.

*Schultze* and *Fischer* regard this case as a mixed form between an ordinary typical acromegaly and dystrophia adiposo-genitalis.

Another type is found by the case described by *Pel*, a type that I would describe in detail. The case was that of a sixteen-year-old youth. Since birth the size of the hands and feet had been strikingly large and they gradually increased in growth; especially of late, after a febrile affection, they have become of enormous dimensions. In this increase in size the increase in the dimensions of the individual bones of the extremities at the distal parts was quite extraordinary. Thus the forearms were 29 cm. long, the circumferences of the elbows about 27 cm. the middle finger about 11 cm. long, the thumbs 7–7½ cm., the circumference of the knee 40–41 cm., the length of the feet about 31 cm., the left leg weighed 4.85 kg., the right 5.1 kg. With all this the total height of the body was not very great (172 cm). The body weight was 50 kg. The head was small, only the nose and the tabular part of the occipital bone were somewhat larger, the teeth, especially the upper incisors were strikingly large. The dimensions were eunuchoid (lower length 112 cm.), the genital organs were entirely infantile (penis 5 cm.), the secondary sexual characters were not developed. X-ray examination showed that the sella turcica was widened, and that only the body parts of the extremities were so considerably enlarged. From youth on there had existed pains of a lancinating character; lately there were very profuse sweats, great muscular weakness, and sensitiveness of the periosteum of the long bones to pressure. It is further noteworthy that veins of the enlarged parts were markedly dilated. A nearly analogous case was recently observed in the Hochenegg clinic and was exhibited by *Demmer* before the Gesellschaft der Ärzte in Vienna [Vienna Medical Society]. *Pel* termed this case "acromegalie partielle avec infantilisme."

Another type is described by *Babonneix.* The case was that of a seventeen-year-old epileptic, 174 cm. tall, two years ago gradual beginning of abnormal growth of the extremities. The hands became strikingly long, the feet "laughably" voluminous, this together with alteration of the disposition, polyphagia and polydipsia; pubic hairs sufficiently developed, genitalia strikingly well developed, especially the penis and testicles, the frontal sinuseis remarkably large, eye-grounds normal, sella turcica not enlarged. *Babonneix* speaks of an acromegaliform syndrome A similar case was exhibited by *Mossé* before the Société de neurologie of Paris, in May, 1911.

Still another type is described by *Renon* and *Delille.* A sixteen-and-one-half-year-old girl who was normal up to the sixteenth year of life, from then on eye-disturbances, headaches and backaches with vomiting, increased growth. Now 168 cm. tall (lower length 103 cm., span width 180 cm.) outbreaks of sweat, obesity especially in the loins and on the abdomen, breasts poorly developed (fat is painful). Slight hairiness of the pubic region and axillæ. Has not as yet menstruated, sella turcica much enlarged, optic atrophy. The authors regard this case as a polyglandular disturbance.

Finally there are reports as to the occurrence of acromegaly in *early* childhood. *Salle* reports the following: The nose of a new-born infant was strikingly large, the chin prominent, the auricles large, flap-like, the tongue large. The relation of the extremities and of the head to the total length was that of a two-year-old child. Hands and feet especially large, fingers and toes strikingly large. Ossification corresponds to that of a three- to four-year-old child. The child died at the age of two and one-half months. The sella turcica was very large, the hypophysis was deformed in the shape of a bean through the projection of an exostosis into the sella turcica; it was as large as that of an adult, the enlargement affected especially the glandular part. Microscopically was found a very considerable richness in eosinophilic cells, such as is found in adults but not in children.[1]

Finally *Hutinel* describes a case with enlargement of the acra in a thirteen-and-one-half-year-old boy.

The cases set forth suffice to indicate the great multiplicity of the forms of early acromegaly. In one is found a large tumor of the hypophysis, in the others the sella turcica is not at all abnormally large; but despite this latter fact I would not doubt that in these cases (*Arnold*, *Pel*, *Demmer*, *etc.*) the diagnosis acromegaly is certain or at least hardly doubtful. Further, the deformation of the bones is also very varied. A manifestation that apparently may occur in early acromegaly in an especially well-marked manner, is the entirely irrelative increase in size of the bones of the extremities in a distal direction. Very diverse too is the porportioning, in that in many cases the eunuchoid proportion is very prominently in the foreground; then again the condition of the genitalia is very different too; in some cases there is hyperplasia, in others hypoplasia and faulty development of the secondary sexual characters, even association with eunuchoid obesity; then, as in the case of *Schultze* and *Fischer*, hypoplasia of the genitalia and obesity, but marked hairiness (hyperplasia of the suprarenals).

The cause of this great multiplicity of type can perhaps be seen in the fact that the child organism or the ductless glandular apparatus of children reacts to a hyperfunction of the hypophysis in a very much more diverse manner than that of adults. Especially the developing genital glands that are involved can behave differently in that here the interstitial glands may be damaged, and thus bring to the total picture admixture with features of eunuchoidism. Then again dependent to a large extent on the behavior of the genital glands is the premature, normal, or delayed closure of the epiphysial junctures. Also the dimensioning of the body may be influenced on account of this. I would, however, treat of one point with emphasis. In some cases the diagnosis may very well be doubted, in fact in some cases it is even made by the respective authors with reserve. In other cases, however, there is no room for doubt; and we must reckon with the fact that acromegalic alterations in the extremities may occur also in youth, *and that therefore the hyperfunction of the hypophysis in early youth does not necessarily lead to gigantism.*

**Differential Diagnosis.**—The point of difficulty in the diagnosis of acromegaly lies in the disproportionate growth of the peripheral parts, not in the enlargement itself, as this may be congenital. There is found for instance a cranium progeneum in many other conditions that have nothing to do with acromegaly (*Sternberg*). Confusion with osteitis deformans of *Paget* is hardly likely on careful examination. In osteitis, the cranial skull is enlarged chiefly in circumference, the long bones soon show curvatures, the alterations in the skeleton are very asymmetrical. In ostéoarthropathie hypertrophiante pneumonique the skull remains unaltered, only the nose may be larger. In this condition we have a dorsolumbal kyphosis, in acromegaly a cervicodorsal kyphosis; the end phalanges show the well-known drumstick form, the nails show curving and longitudinal ridges; while chiefly the region of the knuckles is very much swollen up, the metacarpal and metatoral region, as *Souza Leithe* points out, show but slight increase in volume. Under circumstances there may occur in the osteoarthropathy club-like swellings of the hands and feet, that may have given occasion to confusion with acromegaly (confer the case of *Schultze* and *Fischer*). *Combination with symptoms of Basedow's disease or myxedema* may in the beginning occasion an overlooking of the acromegaly. Early genital disturbances or rheumatoid pains may especially lead to a false path. *Syringomyelia* may also lead to an increase in volume of the extremities, but in this condition there are usually found in addition deformations and the well-known dissociation of the sensation-qualities. In ordinary macrosomia only single members are affected, never both upper extremities and both lower extremities simultaneously. Cases in which hands and feet were enormously enlarged I have already discussed in the consideration of early acromegaly (*Pel*, *Demmer*). We must not forget that the acra of the face may begin to become enlarged very much later. *Erb* saw such a case; the enlargement of the extremities had existed for about twenty years before the tongue and nose began to enlarge.

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[1] Also *Benda* (Med. Klin., 1912, 284) regards the histological alterations as typical, but does not regard the fact ruled out that the alterations of the jaws, tongue, and hands, may simply have been inherited.

Finally we must refer to the significance of the demonstration of the enlargement of the sella turcica by Röntgen translumination, as first demonstrated by *Oppenheim*.

In acromegaly there is usually found deepening of the floor of the sella without material widening of the introitus, while in the tumors of the hypophysis without acromegaly dilatation of the introitus and destruction of the clinoid process is commoner, although there are exceptions.

Important for a differential-diagnostic standpoint is finally the circumstance that genital disturbances may occur. *Salbey* reports a case in which oophorectomy was undertaken because of amenorrhea and pains in the back and abdomen. Several months later there developed a picture of acromegaly.

Until lately the treatment was utterly ineffective. Striking results were first brought about by the resection of the hypophysis tumor first inaugurated by *Horsley*, by *Schloffer* and by *v. Eiselsberg* and first happily carried out by *Hochenegg*. I refer to the consideration of hypophysial dystrophy for a discussion of the method of operation. In the first two cases of *Hochenegg* (reported by *Stumme* and *Exner*) there occurred not only a disappearance of the symptoms of cerebral pressure but also a retrogression of the acromegaly manifestations as well. The teeth of the upper jaw again approached each other, the acra became smaller, the skin softer and wrinkly, the menses returned, and the abnormal hairiness again retrogressed; the retrogression of the acromegalic skeletal alterations could also be demonstrated by the X-ray (*Hochenegg*). In two cases, *Exner* saw an enlargement of the thyroid set in after the operation. Since this time a number of other operated cases have been reported, in part with good results (*v. Eiselsberg*, *Kocher*, *Moskovitz*, *Lecène*, *Cushing*, *O. Hirsch*, and *others*). Especially striking was the result in the case of *O. Hirsch*, in which rheumatoid pains disappeared, the acra decreased in size, and the menses recurred and since that time remained regular. *Hochenegg* on the basis of a third case that pursued an unfavorable course, points out that in cases in which the tumor is chiefly extrasellar the chances of operation are always very much less. Considerable destruction of the clinoid processes and slight deepening of the floor of the sella must like myodegeneratio cordis and status lymphaticus be considered in the indications for operation.

I refer again to the cases already described in detail that were operated on by *O. Hirsch*. In one there came about an essential subjective and objective improvement. In the other case, which I saw again after a half year, there had been no improvement at all.

If in cases of acromegaly with high-grade brain-pressure affections a radical operation is not possible, a palliative trepanation or an *Anton's* "Balkenstich" [puncture of the corpus callosum] is to be thought of.

The X-ray treatment of acromegaly was first suggested by *Gramégna* and first practised by *Béclère*. It is stated that retrogression of the symptoms of cerebral pressure and improvement in the visual disturbances have been obtained (see also treatment of hypophysial dystrophia adiposo-genitalis). A result can be expected from thyroid-gland therapy only in cases complicated with myxedema. Concerning the treatment of the more prominent symptoms of complicating Basedow's, I refer to the chapter on Basedow's disease. Otherwise in acromegaly the therapy can at most assuage pain by means of antineuralgics and combat eventually cardiac insufficiency and the decay of strength by means of general roborant measures.

## b. Hypophysial Dystrophy

Hypopituitarismus, type *Fröhlich;* dystrophia or degeneratio adiposo-genitalis.

**Historical.**—The occurrence of cerebral adiposity or of dysgenitalism in tumors of the hypophysis was mentioned already by *Babinski*, *Anderson*, *Shuster*, *Uhthoff*, and *others*.

In the year 1901, *A. Fröhlich* on the exhibition of a case that came from *v. Frankl-Hochwart's* dispensary first coined the diagnostic dictum that rapidly developing obesity, infantilism of the genitalia, and myxedematous alterations of the skin suggest tumor of the hypophysis.

The case reported by *Fröhlich* was that of a fourteen-year-old boy in whom the disease began two years before the presentation, with headaches, vomiting, and rapid increase in weight. There existed a characteristic distribution of fat, such as will be described later, the genitalia remained entirely infantile there was no hairiness of the genitalia, the axillary region and the trunk, and the skin showed slight signs of myxedema. Since that time numerous cases such as this have been reported by *v. Frankl-Hochwart's* assistants, *A. Berger*, by *Erdheim*, *Zak*, *A. Fuchs*, *Bartels*, *Madelung*, *Launois* and *Cleret*, *Babonneix* and *Peisseau*, *Creutzfeld*, *Neurath*, *Bychowski*, *Marinesco* and *Goldstein*, *Jutaka Kon* and *others*, and finally several cases by *v. Frankl-Hochwart.* A series of cases is presented by the author in course of the following exposition.

**Definition.**—*By hypophysial dystrophy we understand a clinical picture characterized by accumulations of fat in definite places or eventually by pronounced obesity of definite localization, such as is found in eunuchs and eunuchoids; further by inhibition of development or by subsequent atrophy of the interstitial glands and the glands of generation and corresponding inhibition of development, or by more or less distinct retrogression of the secondary sexual characters and of the genitalia; further, when the disease occurs in youthful years, by inhibition of growth and inhibition of ossification. Finally, on account of a sluggishness of the entire metabolism, there is often added as a symptom of irritation a polyuria; finally are added also symptoms of pressure on the part of the optic nerves. A lessening or a loss of the function of the glandular hypophysis called forth by processes in the hypophysis itself or in the vicinity of the hypophysis may be looked upon as a cause of this condition.*

**Symptomatology.**—One of the most important symptoms is the *obesity*, with a quite definite type of fat-distribution, such as is found also in primary inhibition of development of the genitalia. The agreement in the distribution of fat in the two types (the primary genital and the hypophysial dystrophia adiposo-genitalis) was first mentioned by *v. Noorden.* The accumulation of fat is chiefly localized to the hips, the buttocks, the mons Veneris, and the mammæ.

In the higher degrees of the fattening the abdominal wall is affected especially in its lower part, where there may develop thick fatty layers. These were seen in several cases; when they were removed the patients felt considerably relieved. The supraclavicular and infraclavicular fossæ may become quite covered over by pads of fat. There is found moreover a collar-like collection of fat on the neck, and as *Launois* and *Cleret* call them, fatty cuffs on the malleoli. The obesity may attain an excessive grade, but it attracts attention also when it is developed only relatively slightly on account of its characteristic distribution. Moreover, it is frequently emphasized in the literature that in spite of the slight ingestion of food, even in spite of the development of a certain cachexia, antemortem, the retrogression of fat was only very slight. I shall later report a case (case Sch, Observation XXXVII) in which a marked adiposity developed in a short time. Then attacks of cerebral vomiting occurred several months, on account of which the ingestion of food was prevented sometimes for days. The boy now lost in weight, it is true, but on account of the residual cushion of fat on the mons Veneris and the delicate texture of the skin the type remained still unmistakable.

There also exist cases of hypophysial dystrophia without obesity. *Rennie* reports such a case and remarks that he was unable to find a similar case in the literature. Probably in such cases the abnormal distribution of fat would, however, be recognizable. Such a case is reported by *Kümmel*. I also shall later report such a case (Observation Gr, XLV). Moreover, I shall report a case of dystrophia adiposo-genitalia, probably of hypophysial origin (Observation Fr, XLIV) who on his entrance into the clinic was very much emaciated on account of a nutritional disturbance. In him also the fat collection on the mons Veneris was unmistakable in spite of the emaciation. When he came under better condition for nourishment in the clinic, the obesity with the typical fat distribution developed rapidly.

The excessive degree of obesity is regarded as endogenous. This conception is based, as we shall see later, on the investigations of the respiratory exchange of gases, that in some cases of hypophysial dystrophy shows pronounced lowering of the fundamental exchange, although to be sure, in other cases the lowering is not at all considerable.

It is to be expected that in hypophysial dystrophy just as in primary genital adiposity the muscles are permeated with fat, as they are, as is known, in castrated animals. Up to the present this condition has had very little attention paid to it except that *Marinesco* and *Goldstein* report a case of typical dystrophy with microscopically recognizable damaging of the hypophysis through a hydrocephalus, in which the fat-permeation of the muscles was apparently found. At all events *Marinesco* and *Goldstein* assume a specific nutritional disturbance of the muscles.

In dystrophia adiposo-genitalis the skin shows a quite characteristic texture. It is often described as alabaster-like, is remarkably delicate and white, mostly is cool to the touch, and sometimes is dry and exfoliates readily. In some, apparently rare, cases myxedematous-like swellings of the skin are distinctly present. Some cases are reported to have falling-out of the hair (see Observation XXXIV). On the contrary the trophic alterations of the nails seem to be rare.

The following case shows typical distribution of fat:

*Observation XXXIII.*—J. L., ten and one-half years old. Entered the clinic June, 1909. Has a poor heredity. Father and two sisters are insane. An eight-year-old brother is hard of hearing. Three years ago began violent headaches, that gradually increased, and recently there occur, now and then, slight attacks of vertigo. Sometimes the *lad sees indistinctly* and with blurring. Sometime there occur parching *sensations of thirst, polydipsia and polyuria. Obesity has developed only recently.* For two years growth has been at a standstill.

The boy is *rather small* for his age.

Height, 131 cm.

Circumference of skull, 56 cm.

Jugulm-symphysis, 45½ cm.

Chest circumference, 80 cm.

Distance between the spines, 30 cm.

Upper extremities, 62 cm.

Upper arm, 24½ cm.

Anterior superior spine to lower border of patella, 38 cm.

From there to internal malleolus, 31 cm.

The boy is very fat, especially in the pelvic region, on the outer side of the thigh, and on the mons Veneris. The penis is abnormally small, the testicles also small, the mammæ are very rich in fat, genua valga.

The intelligence is normal, the status of the nervous system shows normal conditions, with the exception of nystagmoid twitching in all end-positions. Fundus and perimetry are normal, the development of the hand-skeleton about corresponds to the patient's age no alimentary glycosuria (100 gm. dextrose).

The X-ray examination of the skull shows:

Sella turcica not deepened, but the entrance to the sella is remarkably broad. This makes the clivus somewhat more sharpened.

Adrenalin 0.001 gm. subcutaneously, no glycosuria.

Diagnosis: Dystrophia adiposo-genitalis, probably hypophysial.

I cite the following as a typical case of hypophysial dystrophia adiposogenitalis.

*Observation XXXIV.*[1]—L. S. B. [female] from Russia. Sixteen years old. Entered the clinic Nov. 1, 1911. Family history shows nothing bearing on the case. Nine years ago the *patient sustained a febrile disorder which she states was typhoid fever.* After the recovery the body *weight began gradually to increase.* She eats a fair amount of food since that time, but especially has she noticed an *increase of thirst,* so that she often has to get up at night to drink. She also urinates very frequently. The patient believes herself to have been well otherwise, until about three years ago. At that time she began gradually to complain of *severe headaches,* especially at night. She complained of formications in the hands, and remarked that there was a decrease in the power of vision. Already at that time an eye doctor had forbidden her to read. Lately the headaches have gradually become worse, especially at nights, the patient readily becomes fatigued, and four months ago she remarked one day that she *could not see at all with the left eye.* At the end of May, 1910, an eye doctor diagnosed *bitemporal hemianopsia,* optic nerve atrophy, vision O. D. 10/40, O. S. 10/70. At the end of August, 1911, there was a supplementary report, O. D. 10/50, O. S: Counts fingers just in front of the eye.

At present there are headaches almost daily; for six months there have existed *falling out of the hair,* the nails have not become brittle; however, the patient is almost always listless and indifferent to all things that occur around her, she yawns very much, but sleeps very little at night. According to her statement she sweats hardly at all. There is no vomiting. *As yet she has not menstruated.*

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[1] The case has been also published in detail by *O. Hirsch.*

The patient is small, about 145 cm. The build of the bones is slender, the musculature poorly developed, the layer of fat very abundant. Especially fat are the mammæ, *in which no trace of glandular substance is palpable.* The nipples are small and retracted. Especial accumulations of fat are found *on the hips, on the outer sides of the thighs, and on the mons Veneris. The axillæ as well as the mons Veneris possess only a very few hairs. The genitalia are rudimentary. The labia minora are scarcely developed. The clitoris is very short, hymen intact. The uterus very small,* the ovaries are not felt.

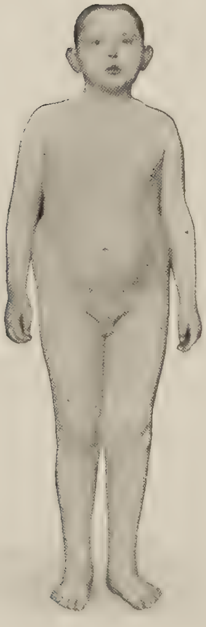

FIG. 51.—Case of dystrophia adiposo-genitalis.

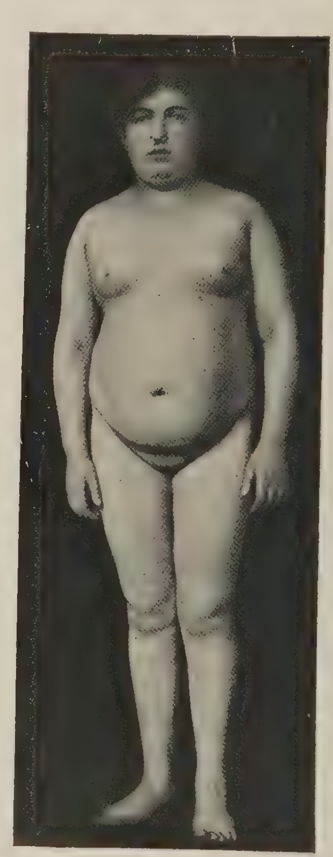

FIG. 52.—Hypophysial dystrophy.

The patient *shows great difficulty in thinking.* She speaks German well enough it is true, but responds to only very simple questions. In Russian she converses rather fluently. She lies in bed very much, and is *indifferent* to her surroundings. During the examination she yawned very much.

The *left eye is amaurotic,* the pupils do not react although the consensual reaction is present. On the right side is *temporal hemianopsia and temporal hemianopic pupillary reaction.* Vision of O. D. 1/10. Both papillæ are sharply demarcated and atrophic. The reflexes are normal. The neck is short, thick, the thyroid not palpable. *The supraclavicular and infraclavicular fossæ* as well as the intercostal spaces are entirely obliterated *by the pads of fat.* The abdominal walls are extremely fat. The fatty tissue of the skin is everywhere markedly sensitive to pressure. The amount of urine is 4000 cc., specific gravity, 1008.

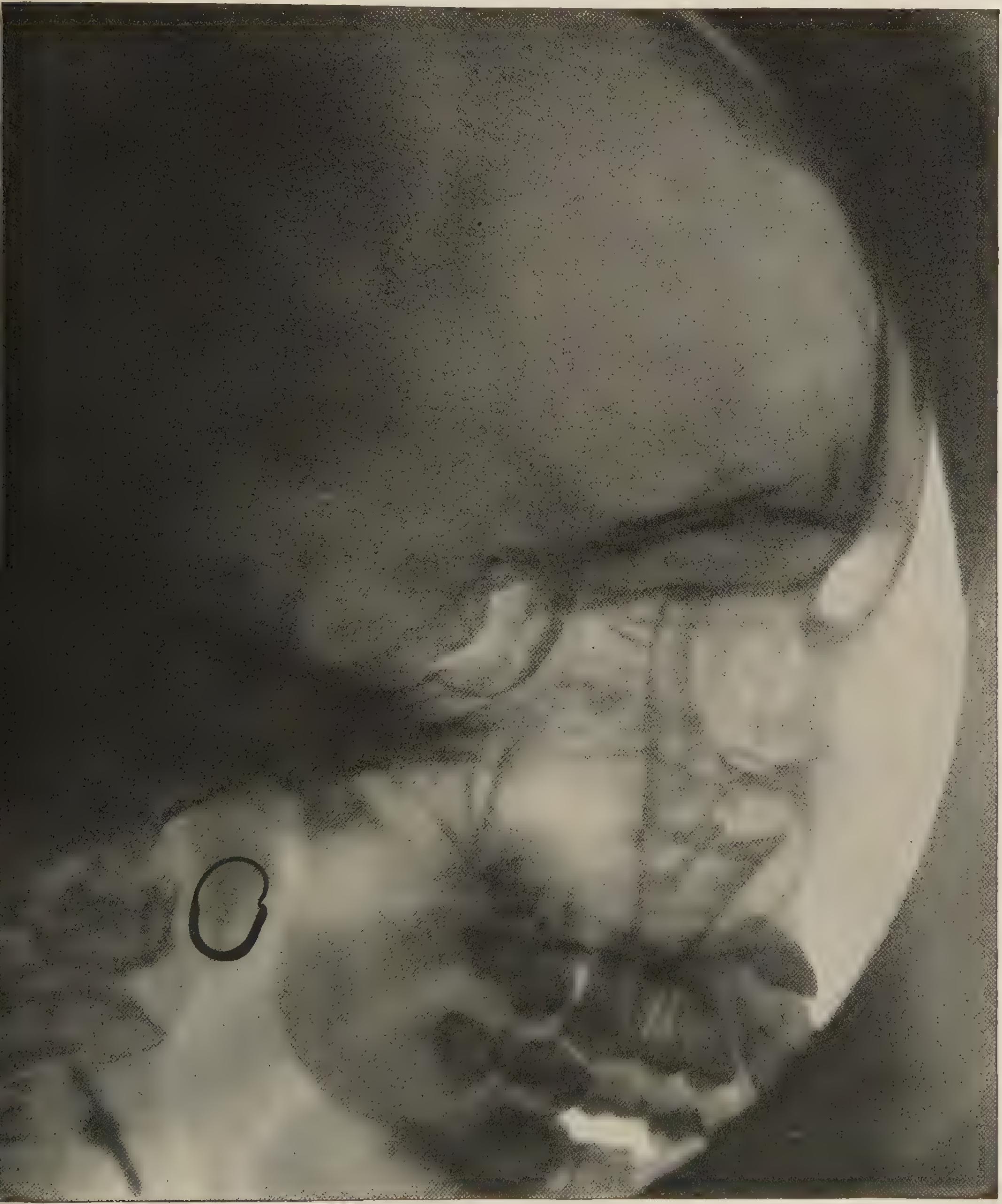

FIG. 53.—Widened and deepened sella in hypophysial dystrophy (Observation XXXIV).

Hemoglobin, according to *Sahli*, 75 per cent.
Leucocytes, 8400 of which

Neutrophiles, 56.1 per cent.
Lymphocytes, 35.8 per cent.
Eosinophiles, 3.2 per cent.
Large mononuclears, 4.9 per cent.
Body weight, 62 kg.
Temperature varies between 36° and 36.6°
Alimentary glycosuria (200 gm. dextrose) negative
The blood sugar is 0.0826 per cent. (*Dr. Bernstein*)

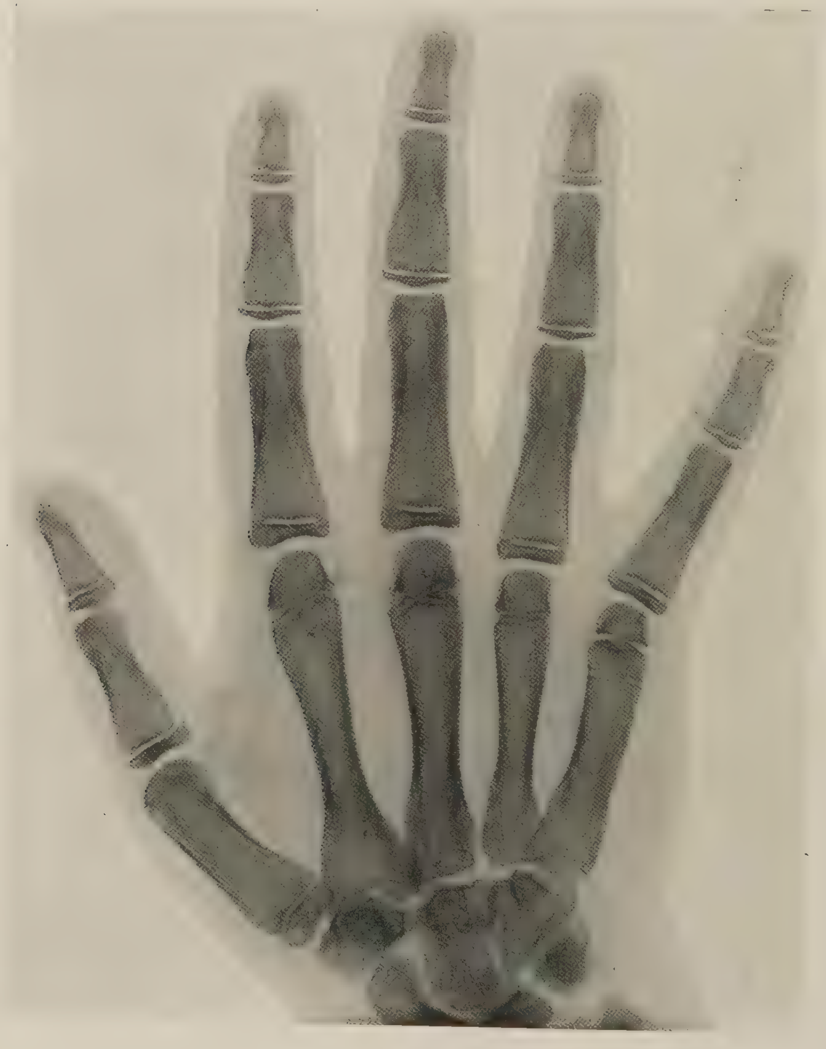

FIG. 54.—X-ray picture in Observation XXXIV.

X-ray.—Cranial vault of normal size and form. Internal surface smooth, sutures are present, sella moderately widened and deepened. Its floor shows an anterior arching forward and a thinning. The dorsum sellæ is thinned, the anterior clinoid processes are retained. Sphenoidal sinuses capacious. The ossification of the hand skeleton about corresponds to the age.

The patient was operated on Nov. 29, 1911, by *Dr. O. Hirsch* at the *Urbantschitsch* clinic, under local anesthesia. The septum was subjected to a submucous resection, both sphenoidal sinuses were opened, the floor of the sella was chiseled off and the tumor partially curetted out, and partially removed through suction through a glass tube. The total mass together with the blood, measured about 45–50 cc. There was no fever for the first two days after the operation, then on the third day the temperature suddenly rose to 39.5°. Vomiting that lasted for five days. There was probably a hematoma in the dural sac of the hypophysis, that went over into suppuration, was in part absorbed, and in part flowed off (*Hirsch*); for several days the fever was very high, 39–40.5°. The third and fourth weeks it gradually declined. At the end of the fourth week the patient was retransferred to the first medical clinic. The patient now makes an entirely different impression, she is incomparably *more lively,* is interested in the surroundings and promptly answers all questions. *The falling out of hair has lessened. The thirst still exists. She yawns much less,* the hairiness of the axillæ and of the mons Veneris has *increased, the visual power of O. D. has risen from* 1/10 *to* 1.67/10. *The headache disappeared entirely after the operation, but reappeared again four weeks afterward.* Very noteworthy are the *blood-findings.* The differential count now shows:

Neutrophiles, 71 per cent.
Lymphocytes, 25 per cent.
Eosinophiles, 1 per cent.
Mononuclears, 2 per cent.
Transitional forms, 1 per cent.

There is now *distinct reduction on the ingestion of* 100 *gm. of dextrose.*

*The patient has lost about* 6 *kg.*

In typical dystrophia adiposo-genitalis is found, in addition to the fattening, an *inhibition of the development of the genitalia and of the secondary sexual characters;* in male individuals the penis remains quite small and may even be entirely buried in the fat cushions (see Observation Sch, XXXVII), the scrotum also remains small, the testicles remain quite diminutive and are usually entirely undescended or partially descended on one or on both sides. Also the prostate remains abnormally small. In female individuals the external and internal genitalia remain quite infantile; the labia minora are developed but very poorly, the clitoris is short, the uterus infantile, the ovaries may be not palpable, the breasts as a rule are indeed very rich in fat, but are poor in glandular substances (see Observation XXXIV). The nipples are small and retracted. Moreover there is either no hairiness of the axillæ, the pubic region and the perineum, or in the pubic region there are only a few bristly hairs. Men remain beardless. The voice does not change or changes very incompletely. The vita sexualis does not develop, and menstruation and ovulation do not occur. In certain cases in which the disease has developed after puberty, there have been reports as to subsequent falling out of the beard hair and the pubic hair, in men impotence sets in, and there is a cessation of erection and ejaculation; in women there is a cessation of menstruation. Libido disappears in both the sexes. There may also occur a partial retrogression of an accessory genital apparatus that once was fully developed (see Observation G, XLV).

**The Metabolism.**—Very few investigations as to the metabolism of hypophysial insufficiency have as yet been made. Already clinical observations would indicate that in hypophysial dystrophy there are considerable alterations in metabolism. We not rarely find the statement that on the one hand, at the beginning of the disease there occur a transitory polyphagia and increased appetite. I refer to S, Observation XXXIV and Sch, Observation XXXVII, to be reported later. On the other hand obesity that develops gradually that in certain cases may attain an excessive degree suggests a reduction in the metabolism.

Also the observation that after operation there is often an appreciable reduction of body weight speaks to the same effect. Statements as to this question are made by *v. Frankl-Hochwart*, concerning the first case that *v. Eiselsberg* operated on with good results. Also in the case of *Hirsch*, previously mentioned (Observation S, XXXIV), a reduction of 6 kg. in weight followed during a short time after the operation.

The investigations as to the *fundamental exchange* or the rest exchange in dogs in which the hypophysis had been removed show unequivocally an appreciable reduction of the respiratory gaseous exchange (*Benedict* and *Homans*, *Porges* and *Aschner*).

The first experiments, in two cases of hypophysial dystrophy as reported in the second edition of *v. Noorden's* book on "Obesity." These experiments which were carried out by *Porges* gave rather normal values. The cases were undoubted cases of hypophysial dystrophy and had been described by *v. Frankl-Hochwart*. Later *Bernstein* found an appreciable reduction in one case. Finally *Bernstein* and *I* have recently investigated a case. I here tabulate the cases thus far investigated.

| Investigator | Case | Age | Height | Weight | $CO_2$ | $O_2$ |
|---|---|---|---|---|---|---|
| Porges, cited by v. Noorden | ......... | 25 | 166 | 70 | ........ | 3.35 |
| Bernstein | G. Wi | 28 | 149 | 65–62 | 2.29 | 2.94 |
| Bernstein and Falta | Fr. | 15 | 121 | 33<br>(25, formerly) | 5.14 | 6.11 |

The few cases do not furnish any certain conclusion. Only in *Bernstein's* case is the respiratory metabolism certainly reduced. This observation hence coincides with the experiences met with in animal experimentation. In case Fr, Observation XXXIV, values of comparison with values furnished by a normal individual equally heavy and tall are lacking.

The observation as to the *carbohydrate metabolism* in hypophysial dystrophy show a noteworthy opposite behavior to that in acromegaly. While in acromegaly, in the great majority of cases, we find the tolerance for carbohydrates more or less reduced, this has not as yet been found in hypophysial dystrophy. On the contrary it seems, so far as investigations up to the present have shown, that the limits of assimilation are raised (*Bondi*, cited by *v. Frankl-Hochwart; v. Noorden*, and *others*). I here publish all of my own observations of dystrophy, equally whether the diagnosis hypophysial disturbance has made certain, or whether it is merely tentative.

*Observation L, XXXIII*, alimentary glycosuria (100 gm.) negative.
*Observation Si, XXXIV*, alimentary glycosuria (200 gm.) negative.
*Observation Si, XXXIV*, after operation, alimentary glycosuria (100 gm.) distinct reduction.
*Observation Sch, XXXVII*, alimentary glycosuria (100 gm. D) negative.
*Observation K, XXXVIII*, alimentary glycosuria (100 gm. D) negative.
*Observation W, XXXIX*, alimentary glycosuria (100 gm. D) negative.
*Observation P, XLIII*, alimentary glycosuria (200 gm. D) negative.
*Observation F, XLIV*, alimentary glycosuria (200 gm. D) negative.
*Observation G, XLV*, alimentary glycosuria (200 gm. D) negative.
*Observation G. Wi., XXXVI*, alimentary glycosuria (100 gm. D) negative, alimentary glycosuria (200 gm. D) trace.
*Observation E. M., XXXV* (200 gm. D) negative.

From the observation on pertinent cases in the literature as well as the cases here reported is elicited the fact that in hypophysial dystrophy there is no *inclination to glycosuria, but on the contrary an abnormal high tolerance for carbohydrates.* A single exception exists in the case of *Link* a case of hypophysial tumor without acromegaly and with diabetes. We shall simply state this fact here and return to it in the discussion of the theory.

Investigations as to the contents of sugar in the blood are up to the present scarce. *Cushing* states that in certain cases he found an abnormally low amount of sugar in the blood. *Bernstein* estimated the sugar in the blood in two of the cases here reported. Both were certain cases, in one of which (Observation S, XXXIV) the diagnosis was verified on operation, in the other (Observation G, XLV) at autopsy. The values were 0.082 per cent. in case S, 0.081 per cent. in case Gr, therefore normal.

Investigations as to *purin metabolism* have as yet been carried out only by *Nowacznski* and *myself*.

In the one case the following was noted:

*Observation XXXV.*—E. M., forty-four years old. Entered clinic March 29, 1912, six years ago sustained a sprain of the lumbar spine by a blow from a stay. Present disease began about six weeks ago with vomiting. Severe headache, twelve days ago diplopia. Flickering before the eyes, weakness of vision. Patient is a heavy drinker; no venereal diseases; for several months increase of weight, reduction of libido and potency.

Vigorous man, sensorium unimpaired, distinct abducens palsy of left eye. Left palpebral fissure narrower than right. Left pupil wider than right. Pupillary reaction on right prompt, on the left delayed. Diplopia on looking toward the left. Nystagmus of left eye on looking toward left. Facialis normal. Tremor of the hands, otherwise no motor or sensory disturbance.

No ataxia. Reflexes normal. X-ray: Sella turcica itself is normal, but the clivus is atrophic as corresponds to the generally increased cerebral pressure.

Alimentary glycosuria (200 gm.) negative.

Diagnosis: Dystrophia adiposo-genitalis due to tumor in the region of the hypophysis.

The investigation of elimination of uric acid on a purin-free diet gave the following values:

0.398–0.406–(20 gm. sodium nucleinate by mouth) 0.434–0.593. The endogenous uric acid value hence lies rather low, at all events the elimination of uric acid after the administration of purin is very low.

The second case was the following:

*Observation XXXVI.*—G. Wi., twenty-eight years old [female]. Entered the clinic May 1, 1912. For one year headache without definite localization. Vertigo, vomiting, ear noises at intervals of months, which for the last three months have occurred almost weekly. Since childhood, slight weakness of vision on the left. For the last six months, decrease of vision on both sides, amaurosis on the left, still some vision remains on the right, for the last months increase of weight. Absent menstruation for the last nine months. Lues denied.

Findings as concerning the lungs, heart, etc., normal; rather fat, especially on the abdomen. Pupils unequal, left larger than the right. The left has lost its round contour, does not react to light, the right reacts slowly. Accommodation on both sides good, globe free, no nystagmus, corneal and conjunctival reflexes present. Fundus normal, right temporal hemianopsia, basal limitation of the visual field, left amaurosis; facial nerve normal. Face hyperalgetic; trigeminus sensibility, temperature-sense, pain-sense, motility, motor power normal. Patellar reflexes lively. Suspicious Babinski reflex on the left. Abdominal reflexes present. No vertigo, no diplopia.

X-ray: Sella turcica dilated quite lightly, especially in the infundibular part. This finding does not speak unconditionally for hypophysial tumor, but may be present in other brain tumors.

Alimentary glycosuria: (100 gm. D) negative; (200 gm. D) trace.

The investigations of the uric-acid elimination on a purin-free diet show the following values:

0.287–0.334–(20 gm. sodium nucleinate by mouth) 0.513–0.206–0.298–0.214.

Hence the endogenous factor lies even lower than in the preceding case. Administration of purin increases the elimination of uric acid but very little.

Quantities of urine up to 2400 cc. with specific gravities between 1005 and 1010.

Investigations as to the gaseous exchange (*Bernstein*)—average of seven investigations

$CO_2$ elimination, 2.29

$O_2$ consumption 2.94

Blood-count: Erythrocytes, 4,600,000

Hemoglobin, 84 per cent.

Leucocytes, 7800 of which:

Polymorphonuclear leucocytes, 74.1 per cent.

Lymphocytes, 19.5 per cent.

Eosinophiles, 0.7 per cent.

Large mononuclears, 5.7 per cent.

At the beginning of the stay at the clinic the patient was very sleepy, and uninterested. Later there developed a clinical picture similar to *Korsakoff's* psychosis, and the patient was transferred to *v. Wagner's* clinic. Increasing weakness, lately Babinksi reflex positive on each side. Facial palsy on the left and pareses of the lower extremities. Pneumonia. Death.

August 6, 1912. Necropsy (assistant *Erdheim*) showed: Cystic hypophysial tumor of the size of an apple, at the base of the brain, at the site of the infundibulum, with protrusion of the tumor into the third ventricle and giving off of the peduncle of the hypophysis from its lower surface. The tumor extends to the circle of Willis and hollows out considerably both the temporal lobes; at the anterior pole of the tumor lies the flattened optic nerves, which are wedged in between the tumor and the anterior cerebral arteries and which show a squeezing together at this place; more on the left than on the right; the lower pole of the tumor lies at the entrance to the sella turcica and dilates it. The dorsum sellæ is moderately eroded, the floor of the sella distinctly eroded, but moderately deepened. In the sella is the hypophysis, which is of normal size with a slight concavity of its upper surface. The tumor is a unilocular thin-walled cyst, in the clear yellowish contents of which float consistent opaque flakes. General adiposity.

A third case, which since this time has been investigated by *Dr. Vias* and *myself*, is later set forth in detail. (Observation F, XLIV). It was that of a juvenile dystrophy, the hypophysial origin of which is only conjectural.

Therefore, in all three cases of the endogenous uric-acid values is at the lower limit of the normal, and the elimination of any purin that is administered is protracted. Of course there exists the possibility that in such cases the absorption of sodium nucleinate is incomplete. After all, even in this respect, there is a noticeable difference from the state of affairs in the cases of acromegaly investigated.

Investigations as to the behavior of the *vegetative nervous* system in hypophysial dystrophy are up to the present very scarce. As far as the excitability of the vegetative nerves through pharmacological means is concerned, I can mention only the following: the glycosuric action of adrenalin (1 mg.) has failed in the cases I have thus far examined (Observations XXXIII and XLIII, see later).

After the injection of 0.01 gm. of pilocarpine in case Si (XXXIV), there was only a very slight sweat. After the injection of pituitrinum infundibulare (2–3 cc. *Parke, Davis & Co.'s* preparation) there could be obtained a marked diuretic action. Hence the excitability of the vegetative nerves seems to be, as in myxedema, generally reduced. Perhaps the nervous mechanism regulating temperature forms an exception to this (see part dealing with the temperature).

Many circumstances speak for the fact that there is a reduction in the tonus of certain vegetative nerves. In all cases we find, for example, statements as to the dryness of the skin and the lessened tendency to sweats.

Here I might mention the statements of *v. Frankl-Hochwart*, and *Fröhlich*, that in hypophysial dystrophy there not infrequently occur vesical disturbances. For the most part they have been referred to the compression of the pes pedunculi by the growing hypophysial tumor; both authors express the opinion that perhaps a reduction of the function of the posterior lobe and lack of pituitrinum infundibulare is responsible. It would indeed be important to pay attention as to the behavior of the vesical disturbances in those cases in which transitory polyuria points to an irritation of the posterior lobe. I shall consider this symptom somewhat in detail.

We find that *polyuria* or *polydipsia* has been mentioned in the history rather frequently. In *v. Frankl-Hochwart's* statistics the picture of diabetes mellitus occurred seven times. When I turn to the newer literature I find that polyuria or at least transitory attacks of thirst are very frequent. I cite the following case:

Case 1 of *Zack*.—Transitory polyuria, with urine of 1000 specific gravity.

Case *Fuchs*.—At times attacks of thirst.

Case *Rosenhaupt*.—An average of 5½ liters of urine. Autopsy showed a sarcoma of the anterior lobe of the pituitary.

Case 1 of *Bartels*.—Twenty-one-year-old man. Polydipsia very pronounced.

Case 1 of *Cagnetto*.—Nine-year-old girl, polydipsia.

Case *Götzl-Erdheim*.—Diabetes insipidus.

Own Observation (L, XXXIII).—Sometimes intense feeling of thirst and polyuria.

Own Observation (Si, XXXIV).—Polydipsia and polyuria, must get up several times at night.

Own Observation (Wi, XXXVI).—At times polyuria, with urine of low specific gravity.

Own Observation (F, XLIV).—Amounts of urine up to 4000, specific gravity 1005–1010.

Also a case of *Frank's* perhaps belongs here: a thirty-nine-year-old corpulent man several years ago attempted suicide by firing two bullets into the right temple. Six to seven liters of urine daily, of specific gravity 1005. Libido lost; X-ray shows one of the bullets in the median line, projecting into the sella turcica from above.

Hence there are found in a great number of cases of hypophysial dystrophy, transitory or more permanent polyuria, indeed in many cases the condition may assume the picture of a severe diabetes insipidus.

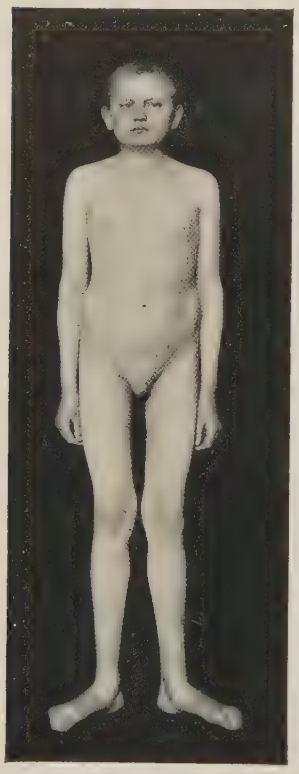

Fig. 55.—Tumor of the subthalmic region with diabetes insipidus.

The combination with polyuria occurs not only in diseases of the hypophysis but also in diseases that affect the neighborhood of the hypophysis (vicinity of the chiasma, subthalmic region, etc.). As we shall consider these cases later in the discussion of the pathogenesis I shall bring to the front the most essential facts in the existing clinical material. *Oppenheim* first pointed out that polyuria frequently occurs in gummatous diseases of the chiasm. Of thirty-six cases of basal luetic meningitis from the literature, twelve had polyuria. *Oppenheim* himself reports two cases with autopsies.

*Spanbeck* and *Steinhaus* found diabetes insipidus eleven times among fifty cases with bitemporal hemianopsia. They themselves report a case of typical hemianopsia, which eliminated 6–7 liters of urine with a specific gravity of 1002. Mercury and iodine treatment brought about complete cure.

I here report a case I saw a long time ago that in many respects is very interesting.

*Observation XXXVII.*—A. Sch., fifteen years old. Entered the clinic Sept., 1909. Father and mother well; no nervous affection in the family. The mother had had four deliveries and three abortions. The first child is entirely well, the second is the patient. The third and fourth children had had transitory illnesses that were without relevance to the patient's condition.

The patient has had a remarkably large head ever since birth. The first tooth appeared in the sixth month, and he began to walk at the age of two years. At this time he was *remarkably tall—a giant child.* At three years of age there developed gradually a convergent strabismus that has existed up to the present time. The boy learned well at school, and was even very intelligent and lively. From the age of twelve years there developed *a gradual lessening of visual power; vertigo* often *occurred*, the boy has very *great thirst, must drink very much and urinated very much.* Also the statement is made by the mother that at this time the boy had a *remarkably large appetite.* He also had to expectorate very much. Gradual increase of body weight became apparent.

In 1908 the patient had been at *v. Neusser's* clinic. There it was noted that there was marked *panniculus adiposis.* Body weight 46.8 kg. Slight concomitant convergent strabismus. The movements of the eye-balls toward all directions are very good, however. The penis is small, no pubic hair, patellar reflexes lively, temporal *paleness of both papillæ.* Field of vision normal. Amounts of urine between 2500 and 4500. Specific gravity about 1008.

According to mother's statement the emaciation began during the mentioned stay at the clinic. Since that stay there have also existed severe *headaches* that occur about twice weekly and are especially localized in the frontal region. During severe attacks there exist marked *sensation of heat and reddening of the skin of the face with outbreak of sweat, vertigo and flickering before the eyes* and mostly *intensive vomiting.* Between these attacks there exists great tendency to sleep, the boy sleeping twelve hours uninterruptedly. According to the mother, there is a common inclination for yawning. The boy states that now and then erections occur. The polyuria is now very considerable. It now is as much as seventy-one times daily, and he must get up often at nights to urinate. *According to the definite statement of the mother, the boy has not grown for a year.*

The boy is tall, the body shows the following measurements:

Jugulum to ant. sup. spine, 38.5 cm.
Jugulum to symphysis, 46 cm.
Vertebra prominens to coccyx, 47 cm.
Circumference of chest, 72 cm.
Circumference of pelvis, 71 cm.
Upper extremities, 68 cm.
Lower extremities, 72 cm.

The face has a more *childish* expression than corresponds to the age. The intelligence is entirely normal, rather more mature than corresponds to the age. Hair is absent in the axillæ and on the pubes, also on the perineum. The boy is *extremely emaciated, especially on the extremities; the most fat is found on the outer surface of the thighs. The mons Veneris* *is very rich in fat. The penis is small, and on both sides the very small testicles remain in the inguinal canal.*

The strabismus remains unaltered. The examination of the fundus shows on both sides *temporal paling of the papillæ.* Perimeter normal.

X-ray examination that had been made even before the patient's entrance into the clinic shows *entirely normal relations of the sella turcica.* Examination of the hand-skeleton shows that the epiphysial junctures and the rudiments of the hand-skeleton correspond fully to the age. The patellar reflexes are lively, but with the exception of the nervous status there is nothing else especial.

Alimentary glycosuria (100 gm. D) negative.

The amounts of urine vary between 4000 cm. and 6700 cm. The specific gravity is 1002–1003.

During the stay at the clinic an attack of headache and vomiting such as is already described occurred. This lasted for two and one-half days, the vomiting was uncontrollable. Ingestion of food during this time nil. Ingestion of fluid very slight, only 1600 cm., or 500 cm., or 1050 cm. *The specific gravity (of the urine) rose to* 1013. The boy during this time lost 3 kg., falling from 37½ kg. to 34½ kg.

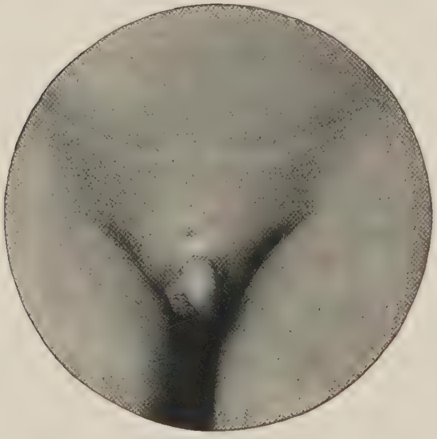

Fig. 56.—Genitalia of Observation XXXVII.

The patient died a half-year after his entrance into the clinic.

*Summary.*—When the patient came into the clinic, he showed the entire picture of dystrophia adiposo-genitalis. As X-ray examination shows the sella turcica to be normal, it may well be assumed that a tumor pressed on the hypophysial peduncle from above. Also the diabetes mellitus fits into the picture, also the undoubted temporal paling of the papillæ, which had not as yet led to a demonstrable hemianopsia. It is further noteworthy that the concentrating power of the kidneys was still present under certain circumstances.

Very noticeable is also the statement of *Strauss* as to cases of diabetes insipidus combined with corpulency of the hypophysial type, with lack of pubic and axillary hair and with hypoplasia of the genitals. In many such cases we are perhaps dealing with developing tumors of the vicinity of the hypophysis, even though there are as yet no other signs of brain tumor.

As an example of this type, I cite the following case:

*Observation XXXVIII.*—S. K., twenty-one years old. Entered the clinic July 12, 1912. Mother of the patient was corpulent, and died of brain tumor. The patient's corpulency began in the thirteenth year of life, together with increased sensation of thirst, the patient sometimes drinking 5 liters of water a day. Corresponding polyuria. This has continued since that time, and only during the last three years has it become somewhat slighter. For years violent headaches, which of late have been increasing in intensity and frequency. The patient has not as yet had sexual intercourse, although according to his statement there exists a certain amount of libido and vita sexualis, and he believes that he would have potentia cœundi. He states, however, that nightly pollutions occur almost never.

About 170 cm. tall, the skin quite soft, mustache and beard are almost completely absent, axillæ show but very sparse hairiness, on the mons Veneris rather good, closing off above in a horizontal line, otherwise hairiness of the trunk and extremities is entirely absent.

Typical eunuchoid fat deposits. Mammæ extremely rich in fat, as are also the vicinity of the hip, and the mons Veneris. The small penis is embedded in a cushion of fat. Testicles of rather normal size and consistency. Genu valgum on each side.

Alimentary glycosuria (100 gm. dextrose), negative.

Blood count: Erythrocytes, 4,240,000
Hemoglobin (*Sahli*), 65 per cent.
Leucocytes, 6500, of which:
Neutrophiles, 65 per cent.
Mononuclears, 28 per cent.
Eosinophiles, 7 per cent.

X-ray examination of the skull shows normal relations.

On freely chosen administration of liquid, an average of 7400 cc. of urine per day. The investigation as to the specific gravity of the urine at different times of the day shows

| | | |
|---|---|---|
| 6–11 A.M. | 1550 cc. | 1008 |
| 11–4 P.M. | 1300 cc. | 1008 |
| 4–9 P.M. | 1900 cc. | 1004 |
| 9–6 A.M. | 2600 cc. | 1002 |

After addition of 15 gm. of common salt to the breakfast

| | | |
|---|---|---|
| 6–11 A.M. | 1200 cc. | 1007 |
| 11–4 P.M. | 1850 cc. | 1007 |
| 4–9 P.M. | 1950 cc. | 1007 |
| 9–6 A.M. | 2600 cc. | 1004 |

*Summary.*—Combination of eunuchoid obesity and deficient development of the secondary sexual characters with diabetes insipidus. Growth-disturbance is absent, as is also any disturbance worth while in the ossification. Probable disease of the brain-stem of unknown nature.

*v. Frankl-Hochwart* emphasizes that in tumors of the hypophysis without acromegaly, often the temperature is established at subnormal values; he himself observed this in three of ten cases. In the case of *Götzl-Erdheim* the temperature varied between 35° and 36°, only exceptionally rising as high as 36.3°. Among my cases this was very evident in case Si, Observation XXXIV, here the temperature varied for a time between 36° and 36.6°; and in case F, Observation XLIV (see later) the temperature varied for a while between 36° and 36.4°; and later even between 35.8° and 36.2°. We could bring this reduction of body temperature into relation with the reduction of the metabolism, as is the case in myxedema. Everything speaks for the point of view that also in hypophysial dystrophy the vegetative functions proceed slower than in normal individuals.

It seems, however, almost as though in hypophysial dystrophy the regulating of temperature may under circumstances show an especial lability. *v. Frankl-Hochwart* has already pointed out the fact that in tumors of the hypophysis without acromegaly sometimes hyperthermia occurs. *Cushing* further reports that the injection of glandular extract into hypophysioprivic animals leads to an increase of temperature, while in normal animals this increase after the injection never occurs. *Cushing* has used this "thermoreaction" as a diagnostic acid, and assumes a state of hypophysial insufficiency in all cases of pituitary disease, in which the increase of temperature occurs after the injection of 2 cc. of a 5 per cent. extract of the anterior lobe of the ox hypophysis.

*Kahn* and *myself* in studies on tetany have several times seen in the acute stages, after the injection of 2–4 cc. of pituitrinum glandulare of *Parke, Davis & Co.* that, as was shown especially actively in investigations on respiratory metabolism, there occurred an increase of temperature to over 38°. Lately *Bernstein* and *myself* instituted experiments on twenty individuals, some of whom were normal and some affected with various diseases, injecting them subcutaneously with 2 cc. and eventually 10 cc. of the glandular extract. Never did there occur an increase of temperature. In one case of very chronic acromegaly, the experiment was negative (case Ad, Observation XXIX). We saw, on the contrary, in case F, Observation XLIV, which will later be reported in detail, no distinct action after the injection of 4 cc. but later on repetition with 5 cc. twice an increase of temperature of more than 2°.

I would not attempt an explanation of this remarkable phenomenon. More extensive observations are necessary to establish the diagnostic significance of the reaction.

Almost regularly in hypophysial dystrophy are found *alterations of the blood picture*.

I have carried out investigations as to this point for years, at first in collaboration with *Dr. Bertelli*, in a series of cases at the clinic.

Through the kindness of *Prof. v. Frankl-Hochwart*, we were permitted to examine some of the cases reported by him. I cite the following observations:

*Observation XXXIX.*—W., twenty-six years old, typical case of hypophysial dystrophy. Examination of the blood in July, 1907. At that time diplopia, reduction of the visual power, bitemporal hemianopsia, since the nineteenth year of life no erections, and no libido, genitalia infantile, pubic hair and axillary hair almost entirely absent. X-ray shows widening of the sella turcica.

Alimentary glycosuria (100 gm. dextrose), negative.
Erythrocytes, 4,800,000
Leucocytes, 5600
Hemoglobin, 7.5 g.

Dec., 1907, operation by *Prof. v. Eiselsberg*, after which improvement of the power of vision and of headache.

March, 1908: erythrocytes, 5,260,000
Leucocytes, 7500
Hemoglobin, 8.2 g.

*Observation XL.*—D., twenty-one-year-old man, Nov., 1909, for ten years gradually occurring headaches and vomiting. For eight years, diminution of the visual acuity. At that time temporal hemianopsia. Pronounced obesity, genitalia infantile, pubic and axillary hairs absent. Destruction of the body of the sphenoid bone and of the dorsum sellæ. June, 1907, operation by *Prof. v. Eiselsberg*. Cyst of the hypophysis, histologically carcinoma. Improvement of the power of vision. May, 1908, occurrence of erections. August, 1908, voice deeper. October, 1909, sparse hairiness in the axillæ and on the pubis. Eye-findings as formerly. Nerve erections. Body weight now 62½ kg. (formerly 65.2 kg.).

Blood count: Erythrocytes, 4,200,000
Hemoglobin, 9.4 gm.
Leucocytes, 8200
Polymorphonuclear leucocytes, 52 per cent.
Large mononuclears, 7 per cent.
Lymphocytes, 37 per cent.
Eosinophiles, 4 per cent.

*Observation XLI.*—O. M., girl, twenty-three years old, Dec. 3, 1909. No hereditary taint, always well, except that from childhood she has been strikingly pale. One menstruation at the age of twelve years, she menstruated regularly between the ages of fourteen and nineteen years, then sudden cessation, with normal genitalia. Now and then moderate pressure in the head. March, 1909, influenza, after which dietary treatment without rest in bed. Increased in weight 8.5 kg. (from 53.5 to 62 kg.). At the beginning of October, 1909, blurring before the left eye, since which time things have remained stationary. No headache, no vertigo, no vomiting, no fainting-spells, no insomnia, no yawning, no disturbance of movements, no rhinorrhea.

Eyes. O. D. normal, O. S. 6/12 fundus normal, L. P. temp. scotoma for white. Bitemporal color hemianopsia. The nerve findings negative. Internal findings and urinary findings negative. Moderate struma, patient is of medium height, strikingly pale, does not make an impression of corpulency, except that a rather large collection of fat is present on the abdomen. Hair of the head abundant, axillary and genital hairiness normal. The fingers seem somewhat puffed up and thickened. Slight development of hair on the upper lip and chin.

X-ray (Docent *Dr. Keinböck*): Sella turcica appreciably enlarged, especially below and behind. The dorsum sellæ is visible only as a small bolt-shadow strip.

Weight 61 kg. Temperature on Dec. 6 and Dec. 7 varied between 36.2 and 36.7.

Blood count: Erthyrocytes, 4,464,000
Hemoglobin (according to *Sahli*), 70 per cent.
Leucocytes, 5900
Polymorphonuclear leucocytes, 60.8 per cent.
Lymphocytes, 30.8 per cent.
Large mononuclear, 4 per cent.
Eosinophiles, 4 per cent.
Mast cells, 0.4 per cent.

*Observation XLII.*—K. L., seventeen years old. Dec., 1909. Up to this time has not yet menstruated, since the autumn of 1906 headaches, decrease of visual power and rapid increase of body weight. Bitemporal hemianopsia. Genitals infantile. Axillary hair poorly developed. X-ray shows dilatation of the sella.

Operation by *Prof. v. Eiselsberg*.

Blood count, Dec., 1909: Erythrocytes, 4,680,000
Hemoglobin, 9.34 gm.
Leucocytes, 9400 of which:
Polymorphonuclear neutrophiles, 56.3 per cent.
Lymphocytes, 31.3 per cent.
Large mononuclears, 7.9 per cent.
Eosinophiles, 3.3 per cent.
Mast-cells, 1.2 per cent.

I tabulate these observations together with those of the other observations reported in detail in this book, in the following list:

| Observation | Erythrocytes | Hb | Leucocytes | Neutrophiles | Eosinophiles |
|---|---|---|---|---|---|
| Observation XXXIX, W before operation. | 4,600,000 | 7.5 gm. | 5,600 | ......... | ......... |
| four months after operation. | 5,260,000 | 8.2 gm. | 7,500 | ......... | ......... |
| Observation XL, D, two and one-fourth years after operation. | 4,200,000 | 9.4 gm. | 8,200 | 52.0 | 4.0 |
| Observation XLI, Olga M. | 4,460,000 | 70 per cent. | 5,900 | 60.8 | 4.0 |
| Observation XLII, K. L., after operation. | 4,680,000 | 9.34 gm. | 9,400 | 56.5 | 3.3 |
| Observation XXXIV, S.... | ............... | 75 per cent. | 8,400 | 56.1 | 3.2 |
| about 5 wks. after operation. | ............... | ................. | ......... | 71.0 | 1.0 |
| Observation XLIII, P..... | 5,000,000 | ................. | 10,000 | 50.1 | 5.5 |
| Observation XLIV, F..... | 4,680,000 | ................. | 5,900 | 64.0 | 5.5 |
| Observation XXXVIII, Ka | ............... | ................. | 6,500 | 65.0 | 7.0 |
| Observation XLV, Gr. .... | 4,800,000 | 57 per cent. | 15,000 | 62.0 | 9.0 |
| later.................. | 3,300,000 | 45 per cent. | 13,900 | 58.0 | 25.0 |
| Observation XXXVI, G. W. | 4,600,000 | 84 per cent. | 7,800 | 74.1 | 0.7 |

Lately there are observations of *Borchardt* in four cases in which he found the red blood cells to be somewhat reduced, the leucocytes at the lower limits of normal, the neutrophiles mostly markedly reduced, the eosinophiles somewhat high, in one case up to 11.5 per cent.

If we summarize all these cases, we find that there is mostly only a slight reduction of erythrocyte count or none at all (or even after operation an increase in the number of erythrocytes) while in all cases there was a not inappreciable reduction of hemoglobin; the leucocyte count is often diminisned, and in one case increased. Most important is the result of the differential count of the leucocytes. Almost in all cases the number of neutrophilic cells is, relatively, markedly reduced, while that of the mononuclears, and especially the lymphocytes, relatively and also absolutely raised. The eosinophiles show in many cases an appreciable increase. After operation the leucocyte picture may revert to normal (Observation Si, XXXIV). In two cases (Observations D and K. L.) there were, however, marked mononucleosis after the operation. Also in these cases the hemoglobin remained markedly reduced after the operation. Perhaps the mononucleosis is the expression of a slight grade of status lymphaticus. The blood-count in general, so far as concerns both mononucleosis and poverty in hemoglobin, is similar to that of myxedema.

I enter more in detail into the consideration of a symptom which up to the present has not been sufficiently regarded in the differential diagnosis. I refer to the inhibition of growth. Already *v. Frankl-Hochwart* emphasized that the cases of tumor of the hypophysis without acromegaly in youth almost always affect small individuals. Almost in all cases in which the disease began in the years between childhood and adolescent life is remaining behind in growth reported. I here quote what I have been able to find in this subject:

Case of *Berger*.—Began at twelve years.

Case 1 of *Bychowski*.—K. L., seventeen-year-old girl, very small, 132 cm. tall (operated on by *v. Eiselsberg*), cyst of the hypophysis.

Case 2 of *Bychowski*.—Reported very briefly. Growth ceased at the age of thirteen years, 132 cm. tall.

Case 2 of *Nazari*.—Normal development up to between the sixth and seventh years, then remaining behind in growth; at twenty years of age, 125 cm. tall.

Case 1 of *Babonneix* and *Paisseau*.—From eleven and one-half years on, height remained stationary.

Case 1 of *Erdheim*.—Twenty-year-old woman, "body very small."

Case of *Zöllner*.—One hundred forty-five centimeter tall individual.

Case of *Uhthoff*.—Dwarfism with bitemporal hemianopsia.

Case 1 of *Ettore Levi*.—Twenty-and-one-half-year-old woman, from ten years old on cessation of growth, 130 cm. tall, lower length 71 cm., genitalia infantile, sella turcica considerably widened.

Case 1 of *Bartels*.—Twenty-one-year-old man, cessation of growth at the fourteenth year.

Case 2 of *Bregman* and *Steinhaus*.—Seven-year-old girl, "relatively small."

Case of *Mixter* and *Quackenboss*.—Twenty-seven-year-old man who looks as if he were eighteen years old, enlargement of the sella, operation. Epithel. congen. of the hypophysis with cystic degeneration.

Case of *Kümmel*.—Twenty-three-year-old man, looks as if he were fourteen years old, no obesity.

Case of *Leman* and *Van Wart*.—Twenty-four-year-old woman, infantile.

Case of *Bournier*.—Twenty-six-year-old man, 125 cm. tall, eye disturbances since his eighth year, disturbance of growth since his tenth year.

Case of *Rennie*.—Cessation of growth at the same time as the manifestations of hypophysial tumor.

*Own Observation XXXIII (L).*—One hundred thirty-one centimeters tall since ten years old. Has not grown for two years.

*Own Observation XXXIV (Si).*—Sixteen-year-old girl, 145 cm. tall.

*Own Observation XXXVII (Sch).*—At the beginning very marked growth, cessation of growth at thirteen years of age.

Also the cases of dystrophia adiposo-genitalis with brain processes in which a limitation of the function of the hypophysis may be suspected, show the inhibition of growth.

Case of *E. Müller.*

Case 1 of *Goldstein.*—Cessation of growth at the fifth year.

Also Case 3 of *Goldstein* is called "small." Both were diagnosed serous meningitis.

Case 2 of *Neurath.*—Scarlet fever at seven years of age, shortly afterward cessation of growth; at ten years of age 109 cm. (instead of 130 cm.) probably hydrocephalus due to meningitis (see later, case Fr, Observation XLIV).

The following case may be regarded as a case sui generis of *hypophysial dwarfism:*

Case of *Jutaka Kon.*—A thirty-seven-year-old "dwarfishy built man" (147 cm. tall) could not visit the school on account of weakness of the eyes. Now and then epileptic attacks, coarse, glittering face, skin dry, lately increasing mental slowness, no hairiness on the mons Veneris, on the scrotum and on the lips. Genitalia entirely infantile. Autopsy showed a slight hypoplasia of the thyroid gland and an enormous calcified tumor of the infundibulum, that histologically was a teratoma. The teratoma has existed since earliest youth, it was "evidently congenital."

The case of *Benda* was that of a thirty-eight-year-old dwarf. There was found a hazelnut-sized teratoma of the hypophysis. The remnant of the gland was atrophic, the genitalia were infantile. Here likewise there was a teratoma, so that it is probable that it had existed since youth and was responsible for the dwarfism and the genital dystrophy.

The case of *Woods Hutchinson* is correctly regarded by *Breus* and *Kolisko* as chondrodystrophy.

In the case of *Hagenbach* (sarcoma of the hypophysis in an individual 103 cm. tall) the connection between the growth disturbance and the tumor of the hypophysis is, as the author points out, hard to show, as it is not known when the tumor began to form.

*Aschner* describes a case of dwarfism which he regards as hypophysial—entirely incorrectly. In this case there does not exist a single symptom that points to this hypophysis. I regard this case as a true infantilism.

The case of *Hueter*, quoted by *Aschner*, is quite uncertain. *Hueter* himself is of the opinion that the tuberculous disease of the hypophysis, in the forty-two-year-old woman, is of recent date, and therefore has nothing to do with the dwarfism. In this case the sexual organs were well developed. This speaks against the existence of the hypophysial affection since youth.

In May, 1911, I observed a case that perhaps belongs to this category.

*Observation XLIII.*—M. S. P., forty-one years old, from Palestine. Entered the clinic May, 1911. Family history good. The patient states that his genitals have been of the present size since childhood. In spite of the fact that the penis is diminutively small, it is subject to erections. First coitus at the age of twenty-two years. Coitus was then practised several times a month up to the twenty-sixth year. The pleasurable sensation was very great, but there had never occurred an ejaculation. Also now the penis sometimes becomes erect, the erections lasting for six to eight hours; they are associated with intense voluptuous sensations. We ourselves saw such an erection, the penis measuring 3 cm.

For three years the patient has suffered with violent right-sided headaches. There exists a slight right-sided ptosis and paresis of the superior oblique and inferior oblique muscles with diplopia.

The patient is 154 cm. tall; span width 172 cm., lower length 97 cm.; he is somewhat fat and there are abundant accumulations of fat on the hips and on the mons Veneris. Hairs of the beard are entirely absent, and there is very sparse hairiness of the mons Veneris and the axillæ. The penis is diminutive, and there is a slight hypospadias. The scrotum is very small. There is bilateral cryptorchidism.

X-ray. Both clivi sharpened, entrance to sella widened. Floor of sella not essentially deepened.

Examination of the eye-grounds; both papillæ present a washed-out appearance, old neuritis.

Blood count: Erythrocytes, 5,000,000
Hemoglobin, 65 per cent., according to *Sahli*
Leucocytes, 10,000, of which:
Polymorphonuclear neutrophiles, 50.1 per cent.
Large mononuclears, 15.0 per cent.
Lymphocytes, 24.4 per cent.
Eosinophiles, 0.5 per cent.
Adrenalin subcutaneously (0.001 gm.), no glycosuria.

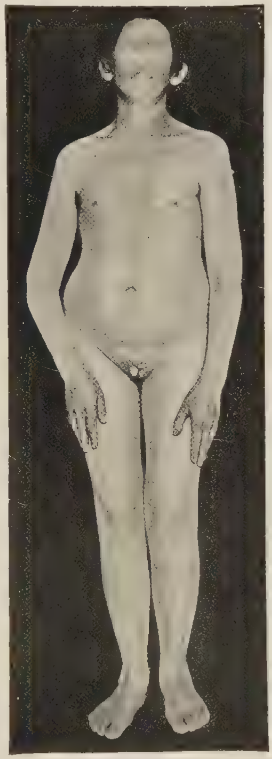

FIG. 57.—Teratoma of the hypophysis.

At first I regarded this case as a eunuchoid, in which a certain function of the genitalia was retained. Also the proportioning of the body seems to me to speak to the same effect. Against pure dysgenitalism speaks however:

1. The disturbance in growth (both patient's parents are large individuals).

2. The disturbance of eye muscles, the symptoms of brain pressure, and the X-ray findings.

As the genital disturbance had action already in earliest youth, the eye-muscle disturbance first becoming apparent only about four years ago, we must think of a gradually developing hypophysial tumor. This may be a teratoma.

Lately *Sprinzels* has shown a case before the Wiener Gesellschaft der Ärzte [Vienna Association of Physicians] that, on account of the interest it affords, I shall describe in detail. It was that of a young man seventeen years old. In the third year of his life after a knock he sustained spasms, probably of a toxic character. Since that time great thirst and polyuria. Since the fifth year of life cessation in growth, sometimes headache, intelligence well developed, gay temperament. Height 106 cm., circumference of head 52.5 cm. physiognomy that of a mature individual, skin soft, smooth, rough and scaly only at certain places, dry, no secretion of sweat. Abundant deposition of fat on chest and abdomen (mons Veneris?), no hairiness on the trunk. Voice childish, several of the teeth belonging to the milk set, genitals correspond to those of a six-year-old boy (erections were observed, however). Amount of urine 3500–4000 cm., specific gravity 1002–1003. Ossification relations correspond to those of a four-and-one-half to five-year-old child. Sella turcica shows no tendency to bone destruction. "A shadow focus coming into the sella from above, and filling out the sella like a bolt, leaving a light zone free," no disturbance of vision. Diagnosis, benign tumor of the hypophysis or in the vicinity of the hypophysis, probably teratoma.

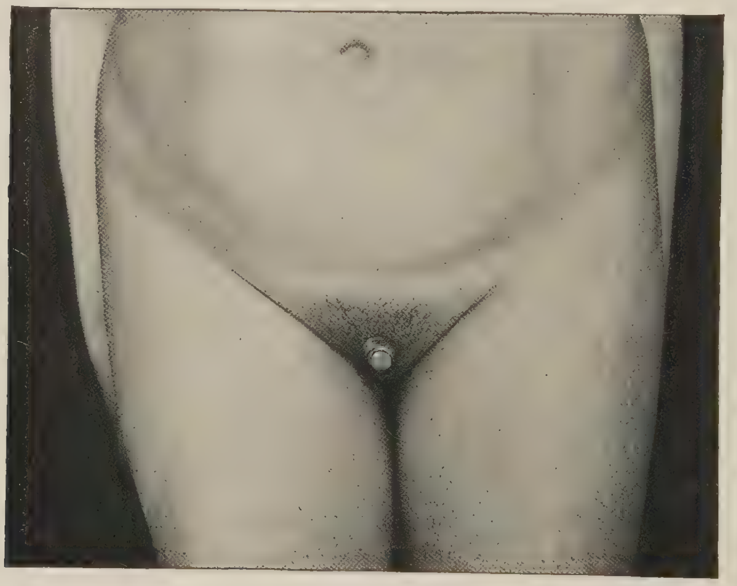

Fig. 58.—Genitalia of Observation XLIII.

I quote the following as a further case of marked disturbance in growth, apparently due to a destruction of function of the hypophysis. We shall find that it will interest us later, in the consideration of the proportioning of the body and the behavior of ossification.

*Observation XLIV.*—Case F., fifteen years old. Entered the clinic September, 1912. The mother of the patient states that the birth was normal, but that she cannot say with certainty when the growth disturbance first began; but that there was rachitis at the eighth year. The child walked late. The abdomen at that time was distended. At all events it is to be supposed that the growth disturbance goes back very far. When the mother was asked concerning fat stools, she answered that these had existed as long as she can remember. Measles at six years of age. In early childhood, patient had frequent sweats. Of late years, he has become thin, and has felt very weak; he became silent and melancholy. He complains of violent vertigo and of headache. For three weeks diarrheal evacuations, that have seemed fatty. The development of the intelligence was apparently normal.

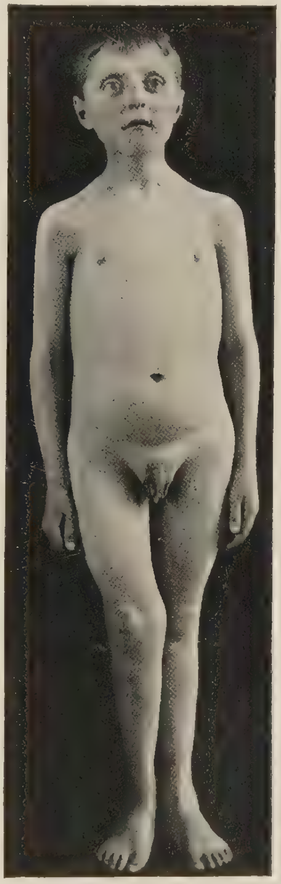

FIG. 59.

The boy measures 121 cm., the span width is 121 cm., lower length (from ant. sup. spine to internal malleolus) 63 cm. The skull has the form of a tower; the greatest circumference measures 61½ cm. The tubera frontalia project to a degree, no saddle-nose, the teeth are very bad, the incisor teeth are much ridged, certain teeth belonging to the milk set. Genua valga. The color of the face is pale, the skin of the entire body is white, remarkably delicate, quite feminine. The patient is thin, but nevertheless there are deposits of fat on the hips and nates, in the hypogastric regions and somewhat more distinctly on the mons Veneris. No rosary formation; no bending of the extremities. No glands palpable. Lung-findings normal. The heart sounds are clear, after several sittings extrasystoles. Examination with the electrocardiogram shows complete dissociation.

The development of the genitalia has remained behind to a marked degree. The penis is small, prepuce well developed. The inguinal canals are pervious for two fingers, the testicles lie in the inguinal canal and come down a little only on marked coughing. They are about the size of beans and very soft; the paradidymis is hardly delimitable. The hairiness on the trunk and genitalia is entirely absent.

*Wassermann* reaction negative. Alimentary glycosuria (200 gm. dextrose) negative.

Blood count: Erythrocytes, 4,800,000
Hemoglobin, 45 per cent.
Leucocytes, 5900 of which:
Polymorphonuclear leucocytes, 64 per cent.
Lymphocytes, 25 per cent.
Large mononuclears, 4½ per cent.
Eosinophiles, 5½ per cent.
Mast-cells, 1 per cent.

The eye examination shows prominent globes, oblique palpebral fissures, dilated pupils, nerves pale, well delimited; the vessels, especially the veins and the peripheral and muscular branches are appreciably convoluted without dilation, old neuritis (?) (*Docent Ulbrich*).

X-ray. Skull strikingly large and high; hydrocephalus, sella of normal dimensions, dilated only at its entrance, its contour retained. The dilatation of the entrance to the sella is perhaps only a partial manifestation of the hydrocephalic extension of the skull (*Docent Schüller*).

The examination of the respiratory gas exchange (*Dr. Bernstein*) shows:

$CO_2$ elimination 5.14 } Average of three well-concurring observations.
$O_2$ consumption 6.11 }

The temperature is instituted at a low level, ordinarily between 36° and 36.4°.

Injection of 4 cc. pituitrinum glandulare intramuscularly shows slight increase of temperature, up to 37°.

Nov. 6. Injection of 5 cc. pituitrinum glandulare intramuscularly at 9 A.M. causes an afternoon rise of temperature to 38.5° (4 o'clock). At 8 o'clock still 38°. On the next morning temperature again 36.2°, no subjective manifestations.

The investigation of the gaseous exchange after the injection shows a very marked decrease of the carbonic acid production and the oxygen consumption. There was appreciable increase of respiratory quotient.

Repetition of the experiment on Nov. 13 with 5 cc. of pituitrinum glandulare (intramuscularly) brought about an increase of temperature to over 38° C.

The amount of urine varied between 2000 and 4000 cc. Correspondingly the specific gravities varied between 1010 and 1006, exceeding 1010 very rarely.

At the beginning several bowel movements daily, later only one or two. The stools are mostly more or less brothy, whitish, glistening like fat, containing, as is shown on microscopical examination, many needles of soap fatty acids and of neutral fat.

Appetite and general condition improve rapidly, also a rapid increase of body weight from 24 kg. to 32½ kg. in the course of five weeks, with distinct prominence of the abnormal distribution of fat on the buttocks, mons Veneris, etc.

The intelligence of the boy is in general well developed, temperament is gay. The complaints as to headache are less.

X-ray examination of the hand shows marked developmental disturbance of ossification. The development of the bone-nuclei about corresponds with that of an eight- to nine-year-old boy.

In this case we are dealing with a chronic hydrocephalus that apparently has led since earliest youth to disturbance of the function of the hypophysis through pressure on the entrance to the sellæ. For the disturbance of hypophysial function: 1. The growth disturbance and the disturbance in ossification and dentition. 2. The genital dystrophy with the typical obesity. 3. Perhaps the "thermoreaction." Whether there exists here a disturbance in metabolism we cannot decide, as there are no values of comparison with normal individuals of the corresponding size and weight. Fitting in with the diagnosis are also the behavior of the carbohydrate metabolism, the blood-count, the hypothemia, and the slight degree of polyuria.

There are as yet no statements in the literature as to the *proportioning of the skeleton and the ossification conditions*. In the study of my cases I made certain observations that seem to me important for the differential diagnosis of the hypophysial dystrophy from the primary genital dystrophy.

The proportioning is sometimes more of an infantile, sometimes more of a eunuchoid type, that is, in the latter case the lower length considerably exceeds the upper length. In a case of *Ettore-Levi* the total length was 130 cc., the lower length 71 cm. In my case L, Observation XXXIII, the total

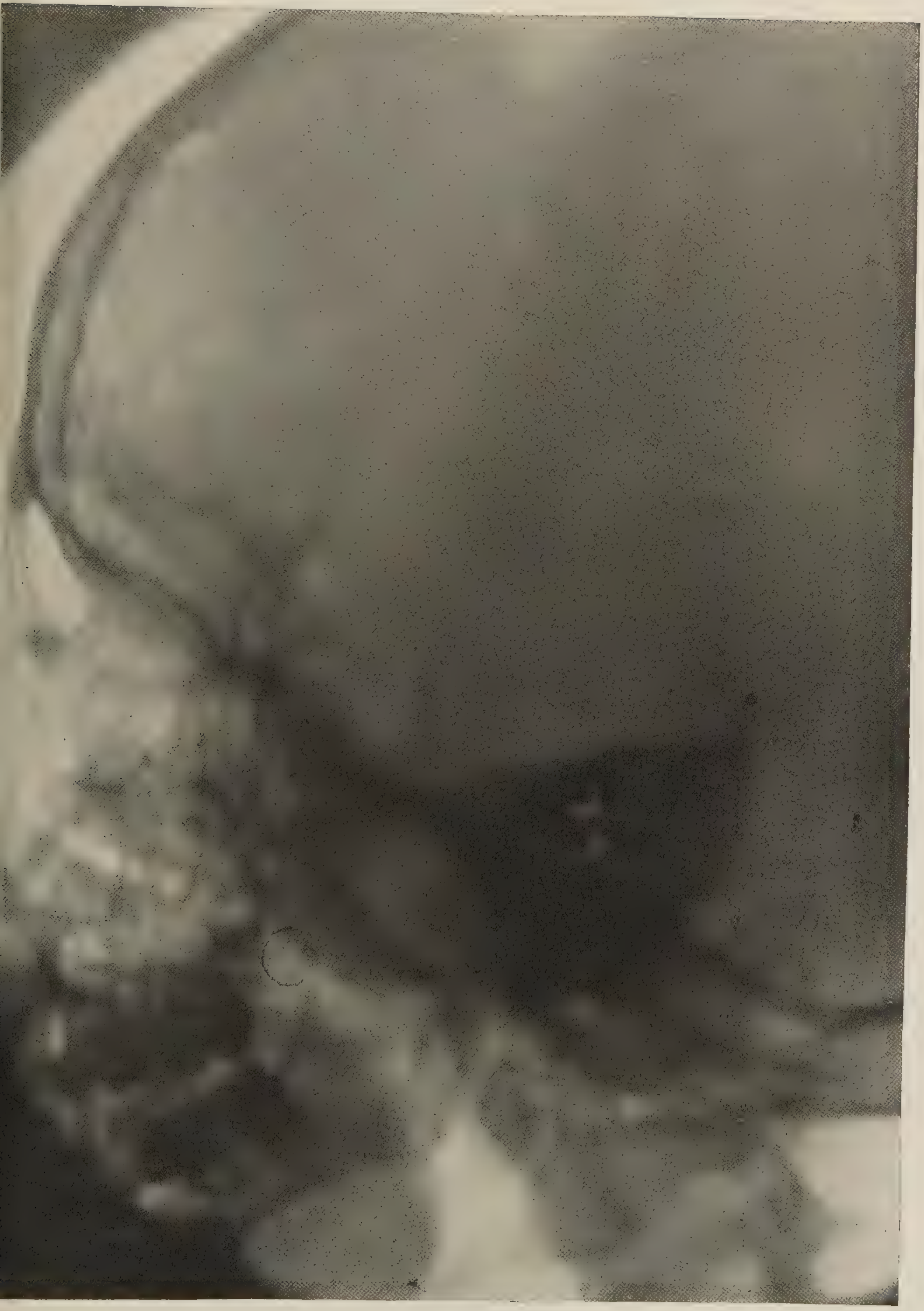

FIG. 60.—Sella turcica of Observation XLIV.

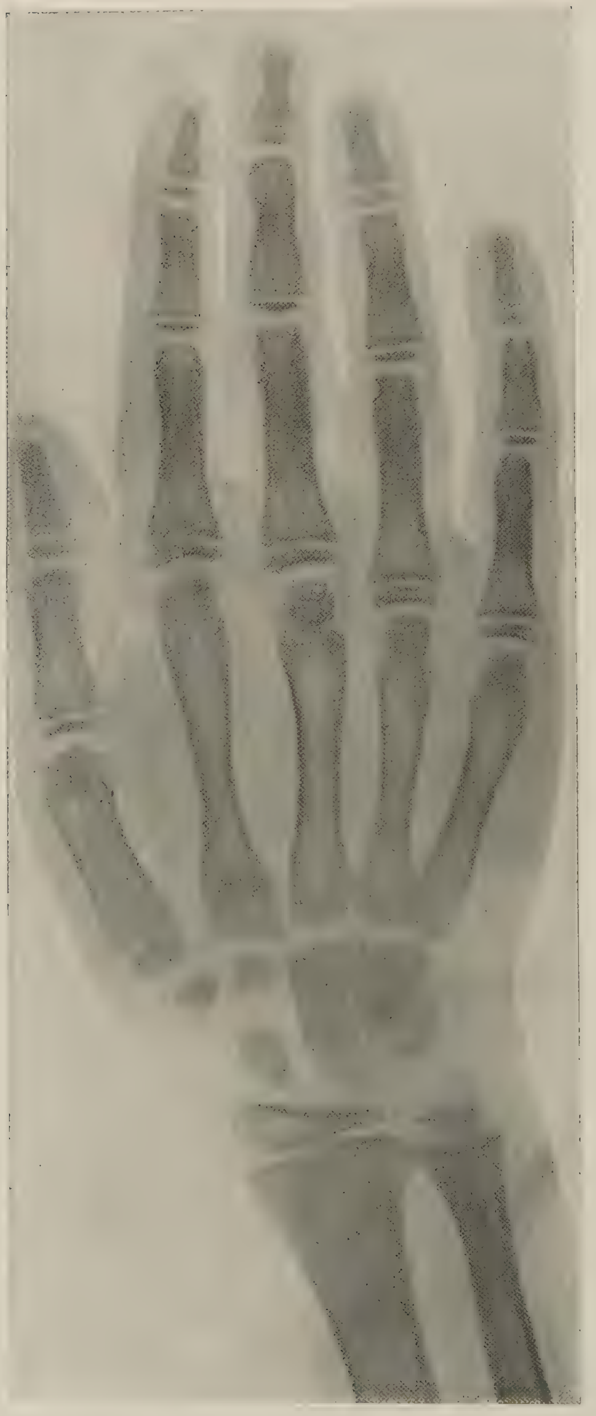

FIG. 61.—X-ray picture of the hand of Observation XLIV.

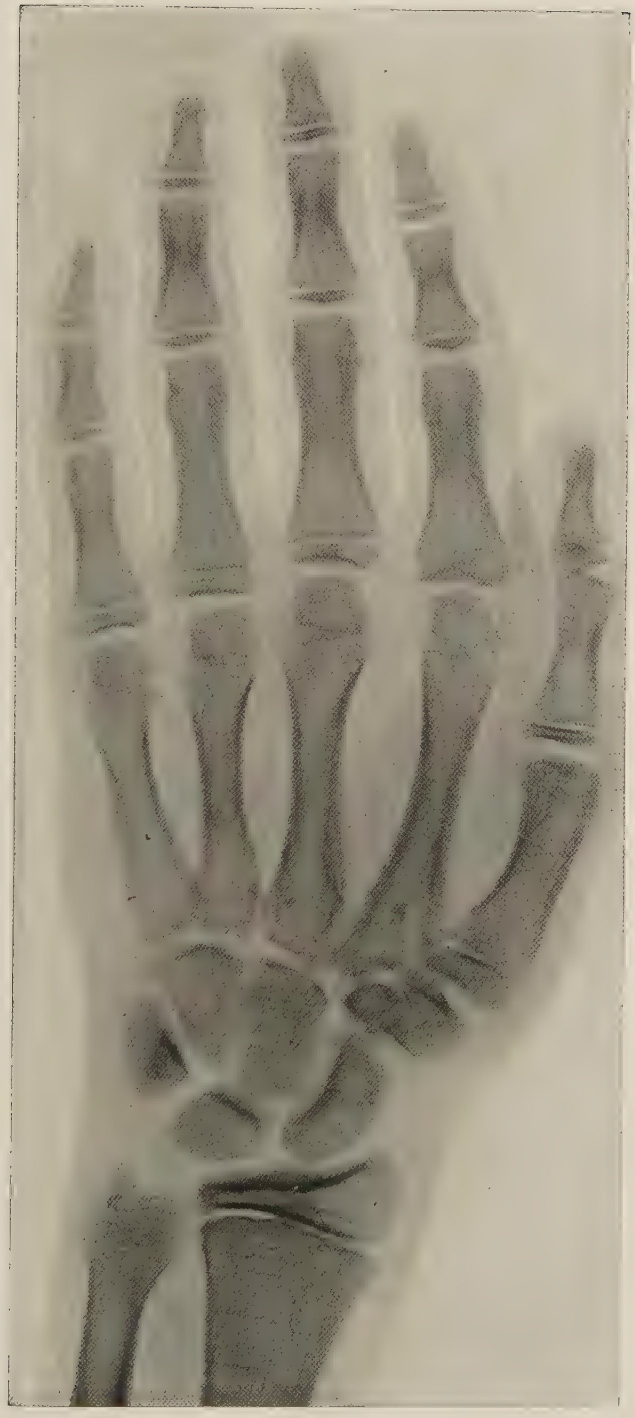

FIG. 62.—X-ray picture of the hand of a normal individual of the same age as Observation XLIV.

length was 131 cm., the distance from the anterior superior spine to the interior malleolus 69 cm.; also in case Si, Observation XXXIV, the lower length is not essentially greater than the upper length. Quite infantile are the dimensions in case Fr, Observation XLIV. On the contrary in case Sch, Observation XXXVII, the lower length again distinctly exceeds the upper length, as it does also in case P, Observation XLIII. It seems to me that here two factors are working in opposite directions. The one is a genital disturbance, this brings about tallness and excess of the lower length over the upper length, the other is a growth disturbance conditioned by the falling out of hypophysial function. According as the one or the other predominates do the proportions approach the eunuchoid or the infantile type. In the severest cases it is indeed mostly infantile.[1]

A distinct difference exists in the ossification conditions of hypophysial dystrophy and eunuchoidism. As we shall see later, in the latter only the epiphysial closure is disturbed; the development of the bone nuclei, however, according to what has been observed up to the present, are not essentially delayed. But the delay in the epiphysial closure is, however, of a high grade and lasts until late life.

How are the conditions in hypophysial dystrophy? Case W. (Observations XXXIX) reported by *v. Frankl-Hochwart* and *v. Eiselsberg*, was, when I examined him, twenty-seven and one-half years old. The first symptoms had set in at nineteen years of age; the condition of ossification was entirely normal. In an eunuchoidism that had set in so late certain epiphysial junctures would have remained open, and there would have been an additional growth of some centimeters. In case L. (Observation XXXIII) and in case Si. (Observation XXXIV) the behavior of ossification approached the normal.

Quite otherwise are the relations in the cases in which the severe disturbance of growth sets in early. In Case F. (Observation XLII) the development of the bone nuclei corresponded to that of an eight- to nine-year-old boy rather than to that of a fifteen-year-old boy. I refer to the X-ray picture of this case as compared with that of a normal fifteen-year-old boy (Figs. 61 and 62).

Hence in these cases the growth disturbance is similar to that in hypothyroidism. From the literature I can quote only the case of *Bournier*, which shows that in the high degrees of growth disturbance also the closure of certain epiphyses is markedly delayed. In the twenty-six-year-old patient the proximal epiphyses of the phalanges and of the first metacarpal bones, and the distal epiphyses of the ulna and radius, are still open. Finally the case reported by *Sprinzel* in which ossification has remained behind much farther than in my case F.

From all this seems to be inferred, that the *disturbance of ossification in*

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[1] I refer to the dissertations in Chapters X and XII.

*light grades of hypophysial dystrophy is not very pronounced, in severer grades it affects in the same manner the occurrence of the bone-nuclei and of the epiphysial closure, while in pure eunuchoidism the epiphysial closure is indeed involved, but this disturbance lasts until late in life.*

To the above-described manifestations is added, according to the process that damages the hypophysis, a series of manifold symptoms. Most common are *tumor symptoms*, such as tend to appear in tumors of the middle fossa of the skull. Most frequent are headaches, that for the most part are not localized; also disturbances of vision (bilateral hemianopsia or simple amblyopia and amaurosis, genuine atrophy, not rarely also choked disc). First there appears bilateral hemianopsia for colors, and only later for white; in quite rare cases there may occur a homonymous hemianopsia owing to destruction of the tract by a tumor (a case of *O. Hirsch's*); in addition vertigo, insomnia, frequent yawning, little sleep at night, however), apathy, finally psychic disturbances, sometimes also nasal discharge of cerebrospinal fluid. With these symptoms are associated paresis of the eye-muscles, disturbances of smell, taste and hearing, vomiting, manifestations of a hydrocephalus, bilateral clonic twitching, eventually paresis of the extremities. Exophthalmus may also occur, owing to penetration of the tumor into the orbit (case of *Pechkranz*).

According to the nature of the picture, *the X-ray examinations* show widening of the introitus to the sella with destruction of the clinoid processes and eventually with deepening of the sellar floor (especially in tumor of the hypophysis), but in extrasellar processes sharpening of the clinoid processes and only later destruction of these (*Erdheim* and *Schüller*), deepening of the impressiones digitatæ in youthful individuals, eventual enlargement of the skull and essential thinning of its bony walls.

Noticeable, finally, are certain alterations of the psyche. *v. Frankl-Hochwart* emphasizes that in these patients there is a remarkable restlessness and resignation, and that in spite of the existing headache they often show a gay temperament. In youthful individuals, at all events, this gay temperament (case F., Observation XLIV, and the case of *Sprinzel*) contrasts markedly with the stupidity and moroseness of hypothyroidism in childhood. In many cases of hypophysial dystrophy there may, of course, also occur a fairly appreciable degree of uninterestedness, which, however, may be much benefited by operation (confer case Si., Observation XXXIV). Now and then there develop also more or less pronounced psychoses. Finally it should be mentioned that also hypophysoprivic dogs show characteristic psychic alterations.

The *pathologico-anatomical* findings that are found in this syndrome are extremely manifold. First of all, there are tumors of the hypophysis itself; a detailed summary of the tumors of the hypophysis without acromegaly is found in the publications of *v. Kollarits* and of *v. Frankl-Hochwart.*

*v. Frankl-Hochwart* has collected ninety-seven cases of tumors of the hypophysis (without acromegaly). Among these are twelve carcinomata, thirteen adenomata,[1] nine strumas, and twenty-seven sarcomata. Among the carcinomata are especially worthy of mention the hypophysial duct flat-celled epithelial carcinomata, described by *Erdheim*. These proceed from the accumulations of pavement epithelium, which lie in process of the glandular anterior lobe that extends into the hypophysial peduncle and which constitutes remnants of the hypophysial duct cut off from the oral ectoderm. (See Figs. 30 and 32.)

Histologically they consist in epithelial nests and concentric layers lying very close to each other. *Erdheim* compares them with adamantinomata, which also originate from cut-off parts of the oral epithelium, as the remnants of the rudiments of the teeth. It may be readily understood that tumors of the hypophysial duct mostly lead first to a dilatation of the sellar introitus.

Then the glandular hypophysis microscopically may appear normal, as in case of *Bregmann* and *Steinhaus*.

Further there were to be observed, according to *v. Frankl-Hochwart*, fifteen cysts, among them the interesting case K. L., that was operated on by *v. Eiselsberg* and that was more accurately described by *Bychowski*. Finally a vascular tumor of indefinite texture, three gliomata, two teratomata, seven tubercles, three gummas, and one case each of steatoma, chondroma and fibroma.

Lately *Marañón* has reported a case of cyst of the hypophysis that for the pathogenesis of hypophysial dystrophy is very important. It concerned a man about forty years old with typical dystrophy. Microscopically the hypophysis was apparently normal, and on microscopical examination more than three-fourths of the glandular part was found to be destroyed by an old focus of hemorrhage.

I report another case that I observed a short time ago:

*Observation XLV.*—G. J., fifty-five years old, tailor. Entered the clinic May 30, 1912. History in part from the wife. Until ten years ago entirely normal. Then marked pains in the frontal region, *attacks of vertigo* and *vomiting*. These pulled him down very much, and the attacks were attended with high fever. He was confined to his bed for six months, then he could again take up his occupation, but since that time his *libido has been markedly* weakened, and finally *disappeared altogether. Also complete impotence came on.* The axillary *hairs gradually fell out.* Since that time attacks of vertigo have been less frequent. In the course of the year 1910 there gradually developed a swelling of the *thyroid* and slight hoarseness. Otherwise there were no other complaints. Dec., 1911, influenza. Remained in bed for six to seven weeks, after which there were lightning-like pains and formications in the [lower] legs. Also the bones were tender. Five weeks ago, according to statement, suddenly a toxic spasm in the right hand and then also in the left hand.

Markedly emaciated *cachectic* individual. Skin pale, dry, scaly, the visible mucous membranes pale. Patient often cannot recollect well, right pupil wider than the left.

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[1] I have already mentioned that not every adenoma must have an increased function and lead to acromegaly.

Reaction somewhat sluggish. Eye-grounds normal. The middle lobe of the *thyroid gland is of the size of an apple,* rather hard, and extends under the sternum, as is seen on examination of the X-ray plate. Circumference of the neck 44½ cm. *Voice slightly* roughened. *Chvostek I* positive. Electric excitability normal.

Blood-pressure (according to *Gärtner*) 90

Blood count: Erythrocytes, 4,800,000

Hemoglobin (*Sahli*), 57 per cent.

Leucocytes, 15,000, of which:

Polymorphonuclear neutrophiles, 62 per cent.

Lymphocytes, 19 per cent.

Large mononuclears, 10 per cent.

Eosinophiles, 9 per cent.

*Pirquet's* reaction negative. Patellar reflexes weak. Hyperesthesia of both lower extremities. Nerve trunks slightly tender. Especial hyperesthesia of the soles of the feet. No hairs in the axillæ. No mustache hairs. *Beard hairs* almost entirely absent. *Hair on the body absent* with the exception of the pubic hair that is still present somewhat copiously. *There are no hairs at all on the perineum.* The entire body is extremely thin, and there is a *cushion of fat still indicated only on the mons Veneris.* The penis is *strikingly small, prostate hardly palpable. Nipples quite stunted.*

X-ray examination of the skull showed considerable *enlargement of the sella turcica to the size of a two-crown piece.* Sellar introitus apparently intact.

Alimentary glycosuria (200 gm. dextrose), negative.

Sugar in blood, 0.081 per cent.

Rapidly increasing cachexia, development of a pneumonia that led to an increase of temperature. *Kernig's* symptom is positive, lumbar puncture negative. On July 5, the blood count was:

Erythrocytes, 3,300,000

Hemoglobin (according to *Sahli*), 45 per cent.

Leucocytes, 13,900, of which:

Neutrophiles, 58 per cent.

Lymphocytes and large mononuclears, 17 per cent.

Eosinophiles, 25 per cent.

On both sides the *struma* decreases *very much in size,* so that on July 1 the circumference of the throat was only 39 cm.

Death on July 23.

Autopsy (*Assistant Erdheim*): *Hazlenut-sized cyst of the hypophysis* with marked pressure atrophy of the pituitary parenchyma and dilatation of the sella turcica. The peduncle of the hypophysis and the base of the skull unaltered. The operculum sellæ deeply retracted. Cerebral hernias with erosion of the vitreous table in the domains of the posterior and middle cerebral fossæ. But the convolutions are not flattened. Growing struma (*Langhans*) proceeding from the middle lobe of the thyroid gland with extensive pressure atrophy of the thyroid parenchyma proper. The thymus small, rich in fat, the suprarenal markedly atrophic, the *atrophy affecting exclusively the cortex, the medulla remaining abundantly developed. Atrophy of the testicles,* marked general marasmus, marked senile atrophy of the upper and lower jaws without almost complete absence of teeth. Lobular pneumonia, etc.

The *microscopical* examination of the hypophysis in the sagittal direction, for which I am indebted to *Dr. Erdheim,* shows the following: The hypophysis is taken up centrally by a single-chambered, smooth-walled cyst, that is filled with a partly homogeneous part, and partly with a part that is in shreds. The cyst for the most part is not lined with epithelium, there being present a single layer of epithelial cells for short distance only.

The tissue surrounding the cyst is ½ mm. thick and constitutes the markedly pressure atrophied, strongly fibrous, glandular tissue of the hypophysis. This is bounded externally by the fibrous capsule of the hypophysis.

The microscopical examination of a piece of the thyroid gland showed a well-limited benign epithelial tumor with numerous cavities filled with colloid, that are separated from each other by septa that are purely epithelial.

In this case there is surely a marked retrenchment of function of the hypophysis of ten years' standing with a gradual increasing cachexia. The disease was ushered in with an unknown infectious process. Perhaps this also affected the hypophysis and gave occasion for the cyst formation. At all events we find since that time a disturbance of the generative function, a gradual partial retrogression of the secondary sexual characters, slight atrophy of the accessory genital apparatus, especially the prostate. Perhaps the marked atrophy of the suprarenal cortex plays a part in the retrogression of the genitals and of the secondary sexual characters.

Worthy of mention in this case is also the uncommonly rapid diminution of the struma. At the beginning this was so hard that originally we thought of a malignant process.

Much cited is the case of *Madelung*. This concerned a nine-year-old girl. At the age of six years, a shot injury from a Flobert gun. The girl has remained behind in mental development, is very quiet. Considerable adiposity that first developed after the injury (at that time the patient remained in bed for five months). The shot had penetrated the sella turcica via the left eye, there was a slight dragging of the left leg and weakness of the left arm.

Besides these tumors originating from the hypophysis there are numerous processes in the neighborhood of the hypophysis in which such cases of dystrophia adiposo-genitalis are found. To these belong tumors that proceed from the brain membranes or the bones, or brain tumors. Especially can all possible brain processes lead to genital disturbances and adiposity, so far as they apparently call forth an increase of pressure in the third ventricle. Already in 1855, *Fr. König* reported a case that seems to me to belong in this category. It was that of an eighteen-year-old girl with undeveloped genitalia; she had never menstruated. The visual power was disturbed. The head was very large. Here was found a hydrops of all ventricles and atrophy of the optic nerves; in the cerebellum, on the left, an echinococcus. This case, on account of the deficient ossification of the pelvis was considered by *A. Paltauf* one of the true dwarfism. For the first exact description of such cases we have to thank *E. Müller*, after *Axenfeld*, already in 1903, had pointed out that tumors at the base of the brain may produce permanent amenorrhea already at the beginning of the disease. In many of *E. Müller's* cases there developed a pronounced obesity. There was observed in the two autopsied cases a tumor of the cerebellum, and a tumor of the occipital lobe respectively. In the cases that he observed only clinically there was probably secondary ventricular hydrops after brain tumors.

*Marinesco* and *Goldstein* described two cases of hydrocephalus with genital hypoplasia and obesity (no autopsy). Like the case of *E. Müller*, the patients were small of stature. *Neurath* further reports cases of hydrocephalus with obesity in children. The genital disturbance was not always distinct. We have to consider however that in children the genital disturbance would not be so prominent as in adolescents. In a review of the pertinent literature I have received the impression that in the slight grades of hypophysial insufficiency first the obesity develops more strongly.

Also case 2 and case 3 of *Babonneix* and *Paisseau* belong to the group just mentioned. In case 2 as in case 1 of *Neurath* the hydrocephalus developed after scarlet fever.

**Pathogenesis.**—The views as to the pathogenesis of the clinical picture described or as to the rôle that the hypophysis plays in it, deviate from one another markedly. Even although at the present we are not in the position to clarify satisfactorily all the manifestations belonging to this picture, I still believe that the later results of pathological physiology and the evident analogies with the diseases of the thyroid we know better have furnished us with a valuable criterion. Let us first consider the results of the *pathological physiology*. The difficult accessibility of the organ and its immediate vicinity to centers important for life has made extraordinarily difficult the experimental studies of the symptoms dependent on loss of the hypophysial apparatus. Only recent years have brought comparative clearness to the solution of the problem. Here, in stating the experiments and their results I shall confine myself to the most important. *Paulesco* was the first to succeed in the complete extirpation of the whole hypophysial apparatus. *He* and *Cushing* used the method of trepanation and pushing inside cerebral hemispheres. Both authors came to the result that the complete extirpation of the entire hypophysial apparatus in dogs leads to death under fall of temperature and blood-pressure, slowing of the pulse, increasing apathy, and deep coma, and they inferred that the hypophysis is an organ important for life, of which the anterior lobe was the part important for life; this because complete extirpation of this alone led to all the manifestations described, while according to *Cushing* total extirpation of the posterior lobe in several cases called forth convulsions and sexual overexcitement, but mostly was without especial action. On the contrary *B. Aschner* on the basis of his very beautiful experiments upheld the opinion that the lethal result described depends on an injury to the tuber cinereum. *Aschner* used the buccal method and found lethal coma on injury to the tuber cinereum and opening of the third ventricle. Less severe injuries or wound infection brings about the appearance of the so-called hypophysoprivic cachexia (marked fall of temperature, apathy, anorexia, polyuria, eventually glycosuria, also adynamia, crying-out of the animals under experimentation, tonic and clonic convulsions and death). On the contrary when the hypophysis is removed without injury to the hypophysial peduncle, the manifestations detailed remain absent, the animals are again lively a few hours after the operation, and remain alive. There develops, especially in youthful animals a condition that in the most important features simulates hypophysial dystrophia adiposo-genitalis. The animals become fat, they remain appreciably behind in development, the dentition and the ossification are markedly delayed, the epiphysial junctures can remain open for a long while, the childish proportions are retained, and the epidermoidal structures such as the hairs and claws show developmental disturbances. The genitalia remain markedly infantile, spermatogenesis is extremely sparse, the sexual instinct is markedly reduced, in female animals rut is weakened and never is there pregnancy. Investigations as to the metabolism of such animals shows that there is great similarity with alterations that *Eppinger*, *Rudinger*, and *I* found in animals without thyroids. The albumin exchange on fasting is markedly reduced. The glycosuric action of adrenalin is reduced, and is associated with a slowing of the pulse and of breathing, reduction of the body temperature, and an appreciable reduction of caloric production. *Benedict* and *Homans* have demonstrated the reduction in the carbonic acid production, *Aschner* and *Porges* the reduction of oxygen consumption, in such animals. The alterations described must be referred to the extirpation of the glandular hypophysis, as extirpation of the posterior lobe alone calls forth no essential alteration. The traces of the epithelial seam of the intermedia that must remain behind in the hypophysial peduncle do not, as *Aschner* supposes, come into consideration.

It is perhaps hardly necessary to describe in detail the great similarity of this symptom complex produced by extirpation of the hypophysial apparatus with that of hypophysial dystrophy. In spite of this I must enter into a discussion of the individual symptoms and their relation to the hypophysis, as just on this point the opinions differ from each other considerably. In this discussion we shall have to keep our attention directed to the fact that, as in acromegaly, the cardinal symptoms due to the deficiency of function of the hypophysis (in acromegaly, the excess of hypophysis function) must be kept separated from the symptoms that are due to the pressure of the growing tumor on the neighboring organs or due to the associated disease of other glands with internal secretion.

To-day the view of most authors is that hypophysial dystrophy with both of these cardinal symptoms—the genital disturbance and the obesity—depends on a loss or diminution of function of the hypophysis (*v. Noorden*, Fettsucht [Obesity] 2nd edition). The relation of both these symptoms to the hypophysis has, however, been called into question. *Erdheim* assumed that the tumor on growing out from the sella actuated an as yet unknown center at the base of the brain, occasioning obesity. *Erdheim* was forced to this conception by the observations that also tumors situated extrasellarly can lead to obesity. Among those authors who refer the obesity directly to the loss of function of hypophysis, there are some who refer the tumor to the loss of function of the nervous lobe, others to that of the glandular. Especially *B. Fischer* is an adherent of the doctrine that it is due to the nervous lobe. He states as a chief argument the fact that the genital disturbance belongs to the early symptoms also of acromegaly. Here it is produced by pressure on the nervous lobe. Also *Cushing*, who formerly in common with *Crowe* and *Homans* brought the obesity into relation with the glandular hypophysis, now agrees with *Goetsch* and *Jacobson* as to the significance of the posterior lobe. Finally, another much discussed question is as to whether the obesity is produced directly by the alteration of function of the hypophysis or secondarily by the functional disturbance of the sexual glands. Lately *B. Aschner* has again taken up *Erdheim's* ~~hypophysis~~ hypothesis and has championed an atrophic center at the base of the brain, the function of which is disturbed by the pressure of the growing tumor. He bases his opinion on the fact that in growing animals total extirpation of the hypophysis never leads to a marked grade of obesity and also not to such distinctly pronounced genital disturbances as in youthful human beings. The result of the operation on tumors of the hypophysis in human beings, so far as concerns the lessening of the obesity and the improvement of the genital function, depends on a release of pressure from the hypothalamic region. *Aschner* sees an especially strong support for his opinions in the experiments, the results of which were recently published, through which it was possible to produce marked trophic disturbance of the sexual glands through injury to the hypothalamic region. Opposed to this view, *E. Müller* has already explained that trophic disturbances in processes at the base of the skull must be set to the account of the compression of the hypophysis, as dystrophy and sexual glandular disturbances are absent in brain tumors without hydrocephalus that have not involved the hypophysis. Also *Marinesco* and *Goldstein* incline to this opinion. *v. Noorden* regards the obesity as thyrogenic (through secondary influencing of the function of the thyroid gland). Finally, also here, as in acromegaly, has been made the attempt to place in the foreground a primary disturbance of the sexual glands (*Schüller*, *Tandler* and *Grosz*). *Novak*, contrariwise, is of the opinion that the results of operation which bring about an improvement of the genital function without essential effect on the obesity, speak for the independence of the obesity from the genital disturbance. We see almost "quot capita, tot sententiæ."

I shall first describe the genital disturbance, as I am of the opinion that the obesity is given its characteristic expression through the genital disturbance. It must here again be mentioned that the genital disturbance in hypophysial dystrophy is throughout not identical with that of acromegaly, as was formerly assumed to be the case, and as had recently again been upheld by *B. Fischer*, *Cushing* and very recently also by *Biedl*. We find on the contrary that at the beginning of acromegaly the genital disturbance is exactly the opposite from what it is in hypophysial dystrophy, and also varies from it later on in the disease. In acromegaly is found at first even increase of the generative function, at all events always a marked accentuation of the function of the interstitial glands or at least no signs of a disturbance. Apart from rare exceptions, that are becoming even fewer, the condition lasts until well in the course of the disease. On the contrary we find in hypophysial dystrophy from the beginning, in addition to the disturbance in the function of the generative glands, disturbances of the interstitial glands. This is the more pronounced the younger the individual affected. The cases in which the disease begins in later life are in addition very rare. In them the disturbance of the generative function is distincter than that of the interstitial glands, indeed it appears as though the retrogression of the once fully developed secondary sexual characters only becomes more distinct when atrophic processes in the other ductless glands, especially the suprarenal cortex, are added, as happened in the case I reported (Observation XLV). Here indeed may occur all transitions to multiple ductless glandular sclerosis with its pronounced late eunuchoidism. *Aschner* mentions that the disturbances of the function of the sexual glands in animals experimented on are found wholly pronounced only when the extirpation of the hypophysis has been undertaken in an animal that is still developing. It seems to me that this does not constitute a contradiction to, but rather an agreement with, the experiences met with in human pathology.

Clinical experience further teaches us that in hypophysial dystrophy the genital disturbances may develop fully even if the pathological process is limited to the hypophysis and entirely intrasellar. I refer to the case of *Marañón* or to Observation XLV. If for the existence of the genital disturbance there was necessary a pressure on a center lying in the hypothalamic region, therefore a forward growth of the tumor, in these cases the occurrence of the genital disturbance would be as inexplicable as in animal experimentation after extirpation of the hypophysis. Also in many cases of acromegaly in which the sellar introitius is dilated, in which growing out of the tumor leads to visual disturbances, perhaps early, and in which there are manifestations of an increased brain pressure, we would then find genital disturbances of the type of hypophysial dystrophy. From all this seems to me to be elicited the fact that loss of function of the hypophysial function alone can lead to genital disturbances of the type of hypophysial dystrophy, just as conditions of hyperfunction of the hypophysis may lead to those of the acromegalic type. The results of the operative treatment of hypophysial dystrophy speak throughout—as I already mentioned in 1908—not against this supposition. The most essential result consists in the relief of the headaches and an improvement in the visual power and manifestations that are intelligible as the result of the release of pressure. In some cases are also observed the occurrence of slight menstrual hemorrhages or of erections. As far as I know, this improvement in the activity of the sexual glands is only slight, and may also be explained by the release of the pressure from the part of the hypophysis that is still capable of functionating.

I must naturally leave open the question of the possibility that through damaging of centers in the hypothalamic region similar disturbances may be brought about in genital function and that in the cases of diseases of the mid-brain that lead to hypophysial dystrophy, without any essential pathologico-anatomical alterations of the hypophysis, the disturbance may perhaps find its explanation in the fact and indeed even in such cases does the possibility seem to me just as discussable—that through such processes the function of the hypophysis is disturbed on account of the characteristic topographical relations, the more so because in such cases we tend to find also other symptoms of hypophysial dystrophy, symptoms such as disturbance in growth, raising of the limit of assimilation for carbohydrates, alterations of the blood picture, etc.

Let us now consider the obesity. The obesity to be observed in cases of hypophysial tumors without acromegaly shows in respect to the distribution of fat full analogies with that which is seen in eunuchs and eunuchoids (*v. Noorden*). Especially important further seems to me the circumstance that even where there is no obesity proper the abnormal distribution of fat is always indicated. This holds true almost always, even in markedly cachectic emaciated individuals. Moreover, we hardly find this distribution of fat expressed in typical manner unless there is present at least some degree of insufficiency. Finally I would again point out that in the predominating majority of the observations reported up to the present the beginning of the disease occurred in youth. Among the cases that have developed the disease later are apparently those in which the abnormal distribution of fat is indeed indicated, but in whom there is otherwise no obesity, but marked emaciation rather.

The loss of the function of the hypophysis hence seems to lead to obesity only under certain conditions. Marked cachexia may prevent the occurrence of the obesity, apart from the suggestion of the abnormal distribution of fat. As example I quote the above accurately reported Observation XLV, or the case of *Sokoloff* in which there was found in the hypophysis a large gumma. For the most part this seems to be the case in sclerotic processes that involve not only the hypophysis, but also other ductless glands. In multiple ductless glandular sclerosis, we come to recognize the rapidly developing cachexia as an important symptom; here is found at most a suggestion of the abnormal distribution of fat, or no obesity, even when the hypophysis is seriously involved (see Chapter XI).

If we assume, as does *Aschner*, in agreement with *Erdheim's* hypothesis, that the higher grades of obesity only come about through the pressure of the superiorly growing tumor on a center lying in the hypothalamic region, the occurrence of these in cases in which the process is limited to the sella would be unintelligible. We would therefore find obesity likewise in those cases of acromegaly in which the tumor grows out of the sella and leads to marked eye disturbance. In these diseases, however, obesity belongs to the rarities, and is even then apparently not of a high grade. Finally, as is even of more weight, we never find in typical acromegaly an indication of eunuchoid fat distribution, such as we always find in the dystrophy. Hence it seems to me, that the obesity depends entirely on the genital disturbance and to be a residual manifestation of the same. Under circumstances we also find in pure eunuchoidism an obesity of quite the same type as in hypophysial dystrophy; the same distribution of fat and in addition the same softness and delicacy of the skin; here, however, there can be no question that there is no process in the hypothalamic region.

Also the remaining cardinal symptoms speak for the supposition that the clinical picture depends on a loss or decrease of function of the hypophysial apparatus. The reduction in the *exchange of gases* fits in well with the results of experimental physiology, as does also the reduction of the *excitability of the vegetative nerves* observed in my cases, and also the *sluggishness of carbohydrate metabolism.* The supposition of *Aschner* as to the genesis of glycosuria in acromegaly is made quite unlikely by the fact that then we would have to expect glycosuria very much more frequently in intrasellar or ex-extrasellar tumors without acromegaly than in acromegaly, while as already mentioned the carbohydrate metabolism shows in all cases the abnormal sluggishness. The case of *Link*, with tumor of the hypophysis (without acromegaly) and diabetes, does not mean anything. An occasional individual may have degeneration of the insular apparatus and diabetes and also a tumor of the hypophysis.

Finally the *growth disturbance!* On a careful review of the literature, I have been able to ascertain that all cases that begin in youth are associated with a disturbance of growth, so that in this respect there is an entire agreement with experimental pathology. I cannot agree with the conjecture of *Aschner* that true dwarfism depends on a lessening of the function of the hypophysial apparatus (see Chapter XII).

On taking into consideration all the facts and convictions set forth above it is my opinion that to-day we are justified in the assertion that *the disease picture of hypophysial dystrophy depends on a loss or lessening of the function of the hypophysial apparatus.*

Finally the question comes up for discussion as to which part of the hypophysial dystrophy is to be ascribed to the involvement of the glandular lobe of the hypophysis and which part to that of the nervous lobe. *B. Fischer* has held the opinion that the obesity and the genital disturbances are due to the involvement of the nervous lobe; *Cushing* has agreed with him and would ascribe to the glandular lobe only the growth disturbance. *Fischer* regards as the principal support of his argument the similarity of the kind of genital disturbance in acromegaly and hypophysial dystrophy. I need hardly again mention that this is not correct. A further support for the view is found in the known tonic actions of the extracts of the posterior lobe on the genitalia, and further the circumstance that in certain typical cases of hypophysial dystrophy, especially in squamous epithelial carcinoma, the sellar introitus is very much distended and the nervous lobe is found to be destroyed, while the glandular part is well retained (for example, case 2 of *Bregman* and *Steinhaus*), although we find a very much larger number of cases in which the glandular hypophysis has been destroyed by cyst formation, gummas, etc., while the nervous lobe was found to be intact. The known tonic action of the extracts of the posterior lobe applies only, as before mentioned, to the nerves of the uterus, and on the contrary an activating influence on the sexual glands is not at all known. Against a direct connection of a disturbance of the function of the posterior lobe with the genital disturbance speaks, however, the following: It is very probable that the polyurias of longer or shorter duration that occur so frequently depend on an irritation of the posterior lobe. Now such polyurias of long duration are found also in cases with pronounced genital disturbance. If therefore we refer the polyuria to a hyperfunction and the genital disturbance to a falling away of the function of the posterior lobe, we would not expect to find them both occurring together. In addition polyuria is found eventually also in acromegaly, in cases with increased function of the genitalia, or at least with failure of a functional disturbance of the interstitial glands, hence it is quite independent of the nature of the genital disturbance.

I must consider the question of *polyuria* somewhat more intimately. Let us remember that transitory or more permanent polyurias, that eventually may show the entire disease picture of diabetes insipidus, are found very frequently in the most diverse hypophysial diseases without acromegaly, and indeed sometimes in acromegaly, and that the same thing is observed also in tumors and other diseases of the brain-stem. Very important fact. for the origin of these polyurias are furnished by experimental pathologys As has been previously presented, there may be obtained from the nervous lobe of the hypophysis an albumin-free heat-stabile extract that possesses in addition to its known action on the blood-pressure, exquisite diuretic characteristics. *Schäfer* states further that the polyuria occurs in the different classes of animals also after feeding with the posterior lobe. Furthermore, implantation of the hypophysis causes an increase of the amount of urine (*Crowe, Cushing* and *Homans*) that again disappears after extirpation of the transplant. Under circumstances the polyuria lasts for several days.

Furthermore, polyuria that may last for many days is very frequent in operations on the hypophyses, as all later authors agree (*Schäfer, Cushing* and *others*). *Schäfer* found a similar polyuria in nonbloody mechanical or chemical irritation of the hypophysis. All these experiments seem to indicate that increased production of this secretion through chronic conditions of irritation (pressure, inflammation, etc.) can occasion a polyuria.

On the other hand it is known that in the medulla oblongata and also further up in the brain-stem, there are found places, the irritation of which may cause marked polyuria lasting for days. As is known, *Bernard's* piqûre is associated with polyuria. If, however, the puncture is done further up, exclusively, polyuria results.

Hence the conditions are such as the conditions with regard to the genital disturbance. *Extirpation of the hypophysis or destruction of a place in the subthalmic region lying above the hypophysis leads to genital atrophy; irritation of the posterior lobe or irritation of a definite place in the brain-stem leads to polyuria.*

Hence one can readily conceive that in tumors or inflammatory processes in the brain-stem or at the base [of the brain], a continuing condition of irritation may be set up in these centers, and on account of it a transitory or permanent polyuria.

The following possibilities seem to me subjects for discussion: Either these polyurias are always the result of a condition of irritation or of hyperfunction of the pars intermedia or the posterior lobe, assuming that tumors proceeding from the glandular hypophysis or from the peduncle, and other lesions, irritate the posterior lobe for a longer or shorter time, and that disease processes localized to the brain-stem also influence the hypophysis in like manner, or that all these polyurias originate through irritation of the nervous centers lying in the brain-stem; or that, finally, it is possible that there is a nervous connection between those centers and the nervous posterior lobe and that irritation of the former spurs on the latter to increased secretion. The decision of this question is not as yet possible. However, it seems to me very improbable that the exquisite diuretic action of infundibular extracts stands in direct relation with the polyurias of the tumors of the hypophysis. Also it seems very probable that in processes in the immediate neighborhood of the hypophysial peduncle, the same process is in play; naturally we must acknowledge the possibility that such polyurias may come about from the centers in the brain-stem, without mediation of the hypophysis.

Finally we must consider the questions as to whether there are any grounds for the fact that also *idiopathic diabetes insipidus* may be referred to an increase of function of the pars intermedia. The question has been recently discussed by *Frank*, among others. As up to the present there are no pathologico-anatomical findings corresponding to diabetes insipidus—and we must also not neglect to mention that not enough attention has been directed to the hypophysis in this respect—it seems to be worth while to approach the question by asking whether there exist any essential differences between the polyurias of idiopathic and of symptomatic diabetes insipidus. *Forschbach* and *Weber* assume that in idiopathic diabetes insipidus the kidneys are especially sensitive and irritable, so that they react to a diet rich in gram molecules [molenreich] with more marked diuresis. *Talquist* and *E. Meyer* formulate their opinion by the assumption that the kidneys are incapable of concentrating the urine. *Breuning* believes, from a collection of the pertinent cases from the literature, that he is able to conclude that (also in symptomatic diabetes insipidus) the kidneys have lost the capacity of concentration. Also *Frank* found it absent in his case. I must point out in opposition to this that this dictum in a general sense does not hold for symptomatic diabetes insipidus. I refer to Observation XXXVII, in which the specific gravity of the urine, after several days of vomiting rapidly rose to 1013. Also the test in case K, Observation XXXVIII, indeed showed, after increase of salt to the diet, an increase in the elimination of salt, but during this day the total amount of urine did not increase. I would here mention some experiments that we carried out on rabbits. In these injection of pituitrinum infundibulare produces marked diuresis. When sodium chloride is administered at the same time there occurred, in spite of diuresis, an appreciable increase of the concentration of the urine. Hence it appears to me that we must leave the question of the genesis of idiopathic diabetes insipidus open.

For the comprehension of the diseases of the hypophysis, a careful consideration of the relations *between the hypophysis and the thyroid gland* seems indispensable, so that I shall here enter into a more intimate discussion of these relations. First some facts experimental. After extirpation of the thyroid gland in young animals there has been observed an enlargement of the hypophysis (*Gley* and *others*). The enlargement affects the glandular part. Vacuoles are found in the cells. Conversely, there occurs after extirpation of a part of the adenoma in acromegaly, an enlargement of the thyroid gland. In myxedema the hypophysis has been found to be enlarged; sometimes, not always. In such cases the enlargement may well depend on strumous degeneration. On the other hand, *Benda* has stated that in Basedow's disease the glandular hypophysis is small. The statements as to the physiological correlations between the two ductless glands evidently do not agree. Of greater clinical interest seem to me the pathological correlations between hypophysis and thyroid.

I already have often referred to this question. Thus in endemic cretinism we have seen that not the thyroid alone, but mostly also the hypophysis is strumously degenerated. *Josefson* reports a case of hyperplasia of the hypophysis in congenital struma of the thyroid gland; also quite other kinds of processes seem to occur spontaneously in the two ductless glands. Thus *Rosenhaupt* reports a case of sarcoma of the anterior lobe of the hypophysis, in which there was also a similar tumor of the thyroid gland. We have also seen that in acromegaly, often manifestations of hyperthyrosis occur, or, especially in the later stages, hyperthyrosis with corresponding pathologico-anatomical alterations of the thyroid gland. Moreover, we shall see later that in multiple ductless glandular sclerosis, the sclerotic process affects almost regularly thyroid gland and hypophysis. A slight degree of the thyroid gland insufficiency does not seem to be rare also in hypophysial dystrophy—at least, a myxedemoid puffiness of the face may be observed, especially in the later stages. Finally, the hypophysis may degenerate also in the later stages of Basedow's disease. I would at least suppose this, because in such cases are found characteristic fat-deposits and swellings of the skin that remain one of myxedema, while the hyperthyrosis still continues and shows a great sensitiveness against thyroidin.

All this points to the fact of an uncommonly intimate pathological correlation between hypophysis and thyroid gland, that is well adapted for the complication of clinical pictures.

**Differential Diagnosis.**—The first question to be decided in the matter of differential diagnosis is as to whether an existing adiposo-genital dystrophy is of hypophysial origin, or whether the individual is a eunuchoid; if the latter is the case, of course all symptoms of brain pressure are absent, and the X-ray plate shows a sella of normal size. But it should not be forgotten that also in hypophysial dystrophy, the sellar alterations and the pressure symptoms may be absent, if gummata, tubercles, or sclerotic processes cause a disturbance of function of the hypophysis. Perhaps also in many cases the examination of the respiratory metabolism might be used for purposes of differential diagnosis. Marked reduction of it would probably only occur when the case is one of hypophysial dystrophy. Of course, many more investigations in this direction are necessary. Probably the ossification conditions are important from the standpoint of differential diagnosis. In primary genital dystrophy certain epiphysial junctures remain open until high age, and there occurs tallness and growth beyond the [age] growth limits of normal. In severe cases of hypophysial dystrophy there occurs, on the contrary, an inhibition of development in the occurrence of the bone-nuclei and also dwarfism, and the epiphysial junctures apparently remain open less long.

The differential diagnosis from tumors of the pineal gland may be attended with difficulty. In the cases of pineal gland tumor that begin in early life the diagnosis is easy, as here is also found a premature development of the genitalia. But even in youthful cases, the tumor of the pineal gland may under circumstances restrict the function of the hypophysis, so that the picture may become admixed with features of the hypophysial insufficiency (see the case of *Raymond* and *Claude*, in the chapter on the epiphysis).

Also the distinguishing of hypophysial dystrophy from multiple ductless glandular sclerosis may present difficulties, as there exist also cases that are associated with marked cachexia. This we saw, for instance, in case G

(Observation XLV). Very marked retrogression of the genitalia and of the secondary sexual characters leads one to think of associated involvement of the suprarenal cortex. Attention should also be especially directed to myxedematous skin alterations and to pigmentations, hypotonia and reduction in the amount of sugar in the blood. When these symptoms are present, we should consider the associated involvement of the thyroid gland or of the chromaffin tissue. In an adiposo-genital dystrophy of hypophysial origin, the exact differentiation of the processes that lead to an impairment of the hypophysis is often very difficult or impossible; and yet this would be of great practical importance for the indications for operation. Here the X-ray examination furnishes important information.

Tumors that proceed from the hypophysial apparatus itself, deepen, when they lie intrasellarly, the floor of the sella. If they proceed from the hypophysial duct they dilate chiefly the sellar introitus, but can also, if they are large deepen the floor of the sella. Intracranial process chiefly sharpens the clinoid processes to a point (*Erdheim*, *Schüller*). Later they may erode them. Then the X-ray would readily lead to faulty conclusions; in such cases erosions are mostly found, however, in other places. Exceptionally a similar destruction—here I follow the dissertation of *Schüller*—may be produced by an aneurysm of the carotid artery, by an endothelioma of the dura mater, or by basal tumors of the middle fossa of the skull. In tuberculous caries or in primary tumors of the body of the sphenoid bone, the infiltration of the sphenoid bone is shown in the X-ray plate, thus enabling differentiation. Finally the clinoid processes may be eroded and sharpened from behind by tumors of the cerebello-pontile angle. The finer details of the bone erosions are alone of value for the X-ray diagnosis, for as *Schüller* mentions, the tumors themselves are only visible in the X-ray picture when they calcify or when they penetrate in one of the pneumatic cavities of the skull. Apart from the X-ray examination, the presence of early pressure symptoms on the part of the more distant cranial nerves or symptoms of a hydrocephalus speak against the primary involvement of the hypophysial apparatus.

**Treatment.**—To-day operation stands in the mid-point of therapy. *Schloffer* and *v. Eiselsberg* in the cases of *v. Frankl-Hochwart*, *O. Hirsch*, and *Cushing* first carried out operation in hypophysial adiposo-genitalis, with partial good results. The methods now used are all intracranial. *Schloffer* and *v. Eiselsberg* made a path to the hypophysis by making a flap of the nose, *O. Hirsch* by operating endonasally. The result consisted at all events chiefly only in the combating of the symptoms of brain pressure; the tormenting headaches disappeared, and the visual power improved, but only in few cases did there result in addition a recession of the dystrophic manifestations, and did the patients lose some kg. of their fat; in certain cases hair even disappeared on the pubis and in the axillæ; in one case erections occurred, in another a slight menstrual hemorrhage was observed some months after the operation. The improvement in the blood picture after operation is noticeable in Observation XXXIV. Also the mental condition changed, and the patient was much more impressionable. Even the combating of the pressure symptoms alone and the saving from complete blindness might in themselves be regarded as a striking result; extreme care must always be taken in considering the indications for or against operation. Apart from the danger of the opinion we should consider that the surgeon should not remove just that part of the hypophysis that functionates, thereby increasing the dystrophic manifestation and eventually bringing on a cachexia. The operation is therefore only indicated in tormenting symptoms of brain pressure or in rapid increase of the visual disturbance. The tumor tissue cannot be radically removed by any of the methods named. Therefore no case without relapse.

The conception of dystrophia adiposo-genitalis as hypopituitarism leads us to expect results from a therapy by administration of hypophysial substance. *Levy* and *Rothschild*, *Axenfeldt* and *Delille*, as well as *Cushing*, claim to have seen good results. In one case I also saw a striking improvement. *Leman* and *van Wart* after the administration of hypophysis tablets saw a growth of hair on the torso. The tumor symptoms (hemianopsia, etc.) are naturally not improved by this treatment. Thyroidin may be used with effect against the obesity. In cases with marked tormenting symptoms of cerebral pressure in which a radical operation is not possible or does not seem advisable, palliative trephining or *Anton's* "Balkanstich" [puncture of the corpus callosum] brings relief. Finally it should be mentioned that *Béclère* saw improvement of the visual disturbance after X-ray irradiation.

*Therapeutic Use of Hypophysis Extracts.*—While in the treatment of hypophysial diseases even the use of preparations from the hypophyses of animals has not as yet won general recognition, yet the extracts from the pars intermedia or the posterior lobe of the hypophysis pituitrinum (pituitrinum infundibulare is a preferable designation) have rapidly acquired a place in gynecology and obstetrics. The investigations of *v. Frankl-Hochwart* and *Fröhlich* have justified our using them in postpartum bleedings. *Foges* and *Hofstatter* in Vienna and simultaneously *Bell* in England first reported the favorable influence on hemorrhages after labor, in which the tendency of the uterus to contraction was heightened by the preparation. The agent may be used intramuscularly as well as intravenously (1–2 cc. in 20 cc. physiological salt solution) (*Hofbauer*). In the numerous experiments of *Foges* and *others*, it was found to be entirely harmless. The agent is especially valuable for Cesarean section. Lately its use has been commended for hemorrhage from the nongravid uterus (*Bab*). It is also recommended in postoperative paresis of the bladder (*Hofstätter*). The voluminous literature pertaining to the subject is found in the works of *J. Novak* and of *C. Heeke*. Finally there are statements as to the treatment of osteomalacia with pituitrinum infundibulare (*Bondi, Pál, Bab, Neu*). Its use as a cardiac and vascular tonic has not as yet been tested. As when it is injected subcutaneously in man it can increase blood-pressure not inappreciably and for a long time tests in this direction seem to me very much to the point, the more so as disagreeable by-actions are very much rarer than when adrenalin is used. As pituitrinum infundibulare increases the respiratory metabolism, *Bernstein* and *I* have tried it in one case of adiposity, without result.

Pituitrinum glandulare has been tested but little. Very interesting is the statement of *Pál* that two cases of osteomalacia that were treated with extract of anterior lobe (*Parke, Davis & Co.*) improved essentially.

## Addendum

The subject of acromegaly, always an interesting one, has been so thoroughly dealt with by the author, and so much has been written about it, especially in this country, by *Cushing*, that the translator feels he has nothing to add. The author is perhaps a trifle misleading in the portion of the chapter that deals with hypophysial dystrophy, conveying the impression that all cases of pituitary tumor that cause this affection are associated with the characteristic fat distribution. Whether this is so is questionable, although authors who have reported such cases do not always take pains to deny that such a distribution is present. *v. Frankl-Hochwart* himself did not find it in the case reports that he reviewed and in some of these reports an emaciation was spoken of. In eleven of his own cases it was present pronouncedly in eight, and was only suggested or indicated in three. *v. Frankl-Hochwart* points out that the cases more nearly approach the classic types the earlier in life the disease sets in.

*Wolfstein* in reporting a case of hypophysial tumor calls attention to the importance of bitemporal hemichromatopsia in the early diagnosis. In this author's case the pubic and axillary hair did not fall out, although there was a sudden cessation of menstruation.

*Sweet* and *Allen* have done apparent total hypophysectomy in dogs, with characteristic changes in the animals but not death. They believe that in the dog the entire gland can be removed without danger to life.

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## CHAPTER VII

## THE DISEASES OF THE EPIPHYSIS (GLANDULA PINEALIS, "ZIRBELDRUSE") [CONARIUM]

**Anatomy and Embryology.**—The epiphysis originates from an extrusion from the roof of the third ventricle. About the fifth month of fetal life there develops between the posterior commissure and the habenular commissure a thin epithelial extrusion that later thickens and penetrates the mesodermal tissue. The epiphysis in many of the animal classes, for instance the reptiles, is very well developed and in the developed human being it constitutes a flat body that arches forward, about 1 cm. long and 0.5 cm. broad, which by the dorsal lip comes into connection with the habenular commissure and by the ventral with the posterior commissure. Between the two lips the recessus pinealis extends from the third ventricle into the gland. In the new-born it is more spherical, and contains regular follicles with polygonal cells, and, toward the recess, glial tissue. Commencing with the seventeenth year there begin signs of involution, increase of the connective tissue and glia; the follicles sometimes form cysts or contain concrements, the so-called brain sand.

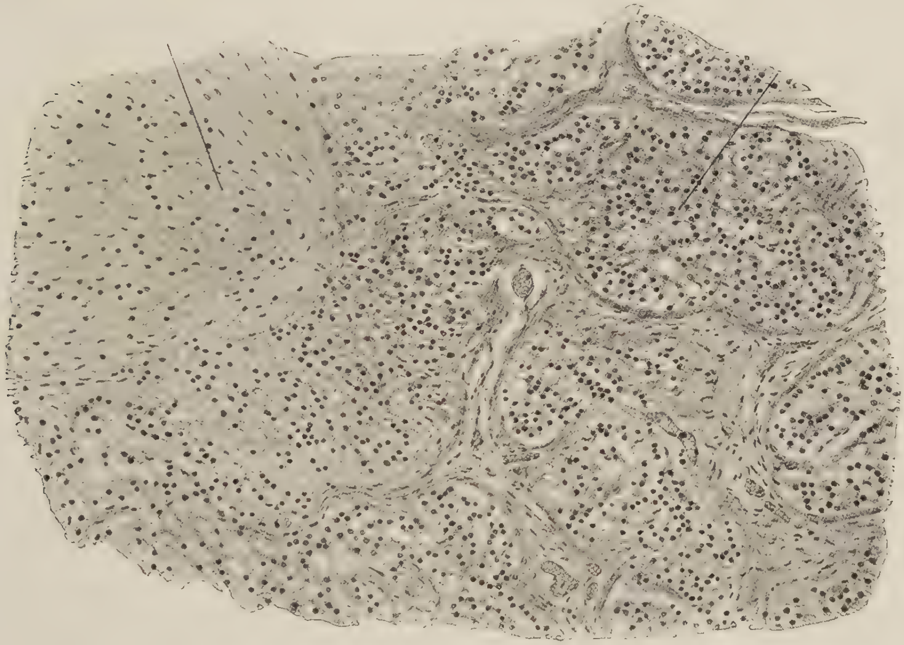

FIG. 63.—Epiphysis of man.

**Pathological Anatomy.**—The diseases of the epiphysis known up to the present time consist chiefly in cyst formations, gummata, and tumors. *Neumann* has collected twenty tumors from the literature and adds two of his own; they were sarcomata, carcinomata, teratomata, gliomata, psammomata and cysts. The individuals affected were chiefly youthful so that, as *Neumann* supposes, the underlying factors might well be chiefly developmental anomalies; they are very much more frequent in the male sex. The teratomata contain hair follicles, sebaceous glands, cartilage, fat, smooth muscle fibers, etc. (*Weigert* and *others*).

**Symptomatology.**—The symptoms that are produced by these lesions of the epiphysis are on the one hand local symptoms, on the other hand characteristic trophic disturbances. The first are caused by the pressure of the enlarged organ on the neighboring brain structures (thalamic, subthalamic region, pulvinar, pons, cerebellum, corpus callosum, etc.), and through congestion in the brain ventricle. If the tumor grows backward, congestion in the fourth ventricle occurs on account of closure of the aqueduct of Sylvius, if it grows forward there occurs hydrocephalus of the third and lateral ventricles. The pressure symptoms consist in motor symptoms of irritation or paralysis, ophthalmoplegias, conjugate deviation, alteration of the pupillary reactions, nystagmus, ataxia, epileptiform convulsions (mostly bilateral), pareses, rigidity of the neck, choked disc or more rarely genuine atrophy, difficulty in hearing, vertigo, headaches, vomiting and eventually slowing of the pulse, lethargy, symptoms that are common also to all the tumors of the quadrigemina.

In addition to these symptoms there occur, if the tumor develops in early childhood, characteristic *trophic disturbances* that consist in an abnormally rapid bodily development and in a premature development of the genitalia, and are uncommonly similar to those which we shall consider under adenomata of the suprarenal cortex. To this group belong the cases of *Östreich-Slavyk*, *Ogle*, *Marburg*, *v. Frankl-Hochwart*, and *Raymond* and *Claude*. Throughout the cases were those of children under ten years of age.

In the case of *Ogle*, the premature development of the genitalia was very considerable. It was the case of a six-year-old boy who died with the manifestations of a brain tumor. Lately the boy had masturbated. The penis was developed like that of a seventeen-year-old youth. There was an abundance of hair on the mons veneris. The testicles were apparently not enlarged. Autopsy showed an alveolar sarcoma of the pineal body. The case of *Östreich-Slavyk* was that of a four-year-old boy who from the third year of life had shown a striking body development; the penis was 9 cm. long, the genitals were covered with hair 1 cm. long. The boy was 108 cm. tall and weighed 20 kg.; these measurements correspond with those of a seven- to eight-year-old boy. The mammæ were hypertrophic and contained colostrum. At the beginning also voracious hunger existed, but later this disappeared.

The case was also described by *Heubner*. The case of *v. Frankl-Hochwart* was that of a five-and-one-half-year-old child, whose body length corresponded to that of a nine-year-old boy; the development of the penis and of the entire genitalia and the secondary sexual characters corresponded with those of a fifteen-year-old boy; frequently erections occurred. The voice was deep, and in addition there was a premature mental development (thoughts about the immortality of the soul); also *Östreich-Slavyk* designated the four-year-old boy described by him as "old-wise" [altklug].

In most cases the conditions of nutrition were stated to be very good. In other cases—apparently in those which develop later—there occurred an excessive adiposity. So for example is the case of *O. Marburg;* here we are dealing with a nine-year-old girl, in whom right at the beginning of the disease (eight months ago) obesity developed, that finally became excessive, especially on the breast and abdomen. Autopsy showed a complex tumor of the epiphysis consisting in tissue of the pineal gland, the ependyma, the choroid plexus, and of glia. In addition to this was found a slight colloid thyroid gland struma, and a slight status lymphaticus; the genital glands and the hypophysis were normal. Also in the case recently described by *Bailey* and *Jelliffe*, that of a twelve-year-old boy, there was obesity; the genitalia were normal. Autopsy showed a teratoma of the pineal gland.

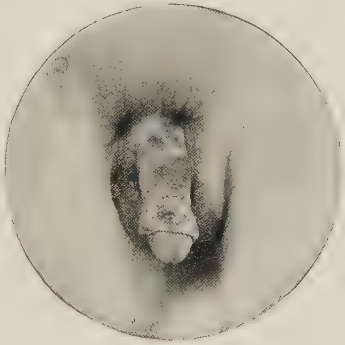

FIG. 64.—Hypertrophy of the external genitalia of a four-and-one-half-year-old boy, 123 cm. tall (penis 6 cm. long, hair on the mons Veneris), according to *v. Frankl-Hochwart*, Ztsch. f. Nervenh., 1900.

In the epiphysial tumors that up to the present have been observed in adults and adolescents there occurred either no especial trophic manifestations (for example in the case of *Neumann*, twenty-seven-year-old man, or in the case of *Askanazy*, nineteen-year-old man) or the trophic manifestations were quite of a different kind. Here there occurred either adiposity, which, as in *Müller's* case may attain an excessive degree (increase of 55 to 79.5 kg. in weight); other cases of adiposity in pineal gland tumor or of tumors that destroyed the pineal gland have been described by *Coats*, *Daly*, *Falckson*, *Kny*, *König*, *Nothnagel* and *others*. Or in other cases there develops a striking cachexia in which the skin may show a pasty consistency. In certain cases polyuria has been observed, in others persistence of the thymus gland, in the case of *Neumann* formation of a goiter. There may also occur atrophy of the genitalia and of the mammæ.

*The significance of all these trophic manifestations is not yet clear.* As far as the premature development that occurs in childhood is concerned, the great morphological difference in the tumors may be explained by the fact that they represent the failure or insufficiency [of function] of the epiphysis. We should therefore understand that normally in childhood inhibitory influences on development proceed from the pineal gland, that gradually fall away or become slighter with the partial involution.

This view has been especially developed by *Marburg*. *Marburg* believed that hypopinealism leads to premature development of the genitalia, hyperpinealism to universal obesity and apinealism to cachexia. The interpretation of adiposity as hyperpinealism is no longer held to be correct, even by *Marburg*. It may very well come about through disturbance of the hypophysial function; one may see very well that the pineal gland tumors may behave in this respect just like other processes that increase cerebral pressure the more so because on account of their position they lead to stagnation in and dilatation of the third ventricle. The interpretation of the premature development as hypopinealism has recently been supported by animal experimentation. *Exner* and *Boese* could not indeed observe a premature development after extirpation of the epiphysis in young animals. *C. Foà*, however, saw after extirpation of the epiphysis in young fowls a premature and extraordinary development of the testicles and some of the secondary sexual characters. Extirpation of the sexual glands in youth produces in male and female animals atrophy of the epiphysis (*Biach* and *Hulles*). *Askanazy* believes that every embryonal teratoma is to be regarded as a sort of pseudopregnancy that should lead to a premature maturation and a premature development of the genital sphere, a view that *Hart* accepts, while *Pappenheimer* opposes it. I do not regard it as impossible that the trophic influences of the pineal glandular tumors in early life go over the suprarenal cortical system [hyperplastic development of], which also leads to premature maturation and premature development of the genitals (see the following chapter).

At least it should be noticed that in one case *Raymond* and *Claude* found hyperplasia of the suprarenal cortex. I will quote this interesting case in greater detail. It was that of a ten-year-old boy. The disease began in the seventh year of life with gradual blindness and increasing adiposity. The boy at the age of ten years was 138 cm. tall (about corresponding to a thirteen-year-old boy) and weighed 39 kg. Much fat had accumulated, especially on the abdomen and on the hips. The pubic hairs were well developed and there was a foreshadowing of a beard on the upper lip. Penis and testicles were small. Histologically the testicles showed no spermatogenesis, but the interstitial glands were very well developed. The less strong predominance of the premature genital development could in this case have been brought about through a restriction in the function of the hypophysis; for the epiphysial tumor, which was the size of an apple, had led to a marked dilatation of the lateral and the third ventricles and to a marked flattening of the hypophysis.

The **diagnosis** of epiphysial tumors in adults is hardly possible, as the symptoms produced are hardly to be distinguished from the tumors of the neighborhood of the corpora quadrigemina.

According to *Marburg* the possibility of an epiphysial tumor should be thought of when there occurs combined symptoms of initial headaches—especially of the occipital region—early choked disc, vertigo, sleeplessness, convulsions, later somnolence, paralysis of the eye muscles associated with ataxia (*Nothnagel*), and disturbances in hearing. What makes the diagnosis the more difficult is that epiphysial tumors, as above mentioned, also lead to dystrophia adiposo-genitalis, probably through limitation of the function of the hypophysis. On the contrary, the diagnosis in childhood is possible, through the combination of general brain tumor symptoms and those of quadrigeminal lesion with those of premature development of the body, the psyche, and the genital sphere, and was first made in vivo by *v. Frankl-Hochwart*. The **treatment** by operation has not as yet been tried.

## Addendum

*Jordan* finds no clear histological evidence indicative of a glandular function of the pineal body, and that if the pineal body in the sheep subserves an important physiological function, this is probably active only during the first eight months of postnatal life. Pineal bodies of sheep older than one year present much variation and degeneration.

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## CHAPTER VIII

# THE DISEASES OF THE SUPRARENAL APPARATUS

**Anatomy and Embryology.**—The suprarenals are paired organs, that sit hood-like on the upper pole of the kidneys. Their breadth according to *v. Neusser* and *Weisel*, is about 40–50 mm., their height 30–35 mm., their thickness 2–8 mm., their weight averages 10.6 gm. in women and 11.6 gm. in men. They are made up of two embryologically independent parts, the cortex and the medulla. The so-called intermediary zone belongs to the cortex. The cortex is made of columns of cells, which cells are filled with glistening granules, most doubly refractile, of a lipoid character. The medulla contains numerous nerves and multipolar ganglion cells, and in

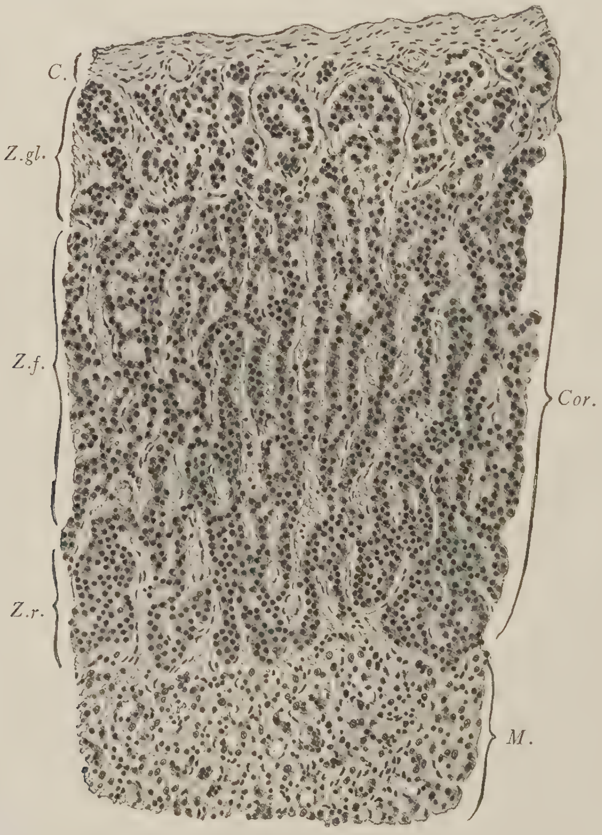

Fig. 65.—Suprarenal gland of man. *C.* = capsule, *Cor.* = cortex, *M.* = medulla, *Z.gl.* = zona glomerulosa, *Z.f.* = zona fasciculata, *Z.r.* = zona reticularis.

addition nests of cells, which take a brown color when they are stained with chromic acid, and a green stain with iron chloride. They are termed chromaffin cells.

From the arteries of the diaphragm, from the aorta, and also from the renal artery, respectively, are given off a branch to the suprarenal glands. These form subcapsularly an anastomosis, from which the cell columns of the cortex are surrounded by a fine capillary network, and which also continues into the marrow; moreover there are the so-called arteriæ perforantes, which run through the cortex and first form a capillary network in the medulla. The suprarenal veins empty into the vena cava.

True accessory suprarenals that are made up of cortex and medulla are rare. On the contrary accumulations of *chromaffin tissue* may exist outside the suprarenals. The larger have been termed "*paraganglia*" by *Kohn.* Such cell accumulations are found on the carotid artery, in the ganglia of the sympathetic trunks and in the solar plexus, in the left stellate ganglion, on the site of giving off of the left coronary artery and superior mesenteric, at the hilus of the kidney, and along the course of the sympathetic nerves (*Zuckerkandl, Kohn*). In the adult the total amount of the extramedullary chromaffin tissue is not smaller than the medullary part; in the new-born it is greater. Accumulations of *cortical substance* can be found at the hilus of the kidney, in the renal substance itself, along the suprarenal veins, and in the internal genitalia. *Schmorl* found them in 92 per cent. of cases, *Weisel* in the genitalia of new-born boys in 76.5 per cent. *Aichel* found them never absent in the broad ligament of new-born girls. Of these also, a portion later retrogress.

Embryological and phylogenetic studies agree with the anatomical that the suprarenal apparatus consists of two independent systems which in the lower classes of animals are arranged segmentally and remain separated permanently. The chromaffin or adrenal system is of ectodermal origin and is part of the sympathetic.

Already at a very early period the primitive cells separate into two different forms, into the primitive form of the sympathetic nerve cells and into the so-called phaeochromoblasts, from which the chromaffin cells originate. The cortical tissue—the so-called interrenal system—develops from the ventral part of the mesoderm and indeed quite in the neighborhood of that place of the celomic epithelium from which the sexual glands originate; suprarenal cortex and sexual glands are laid out in the Wolffian duct, which explains the topography of accessory suprarenals consisting in cortex alone along the entire way that the sexual glands travel, indeed even in the sexual glands and kidneys themselves (*Soulié*). During fetal life the suprarenal is at first larger than the kidney, and at birth is about the same size. Already at an early period a part of the chromaffin cells has broken through the complex of cortical cells to form the medulla. Through the descent of the genital organs small parts of both systems are displaced. This shows that the former complete physiological independence of both systems later gives place to a common function, at least in part (*Biedl*), which fact is also indicated by the previously mentioned relations of the blood-vessels. It is indispensable for the comprehension of diseases of the suprarenals to consider that the two systems for a great part are functionally independent. The higher we go in the classes of animals, the greater become the complexes of the two systems that finally unite to form a single organ, the suprarenal.

## a. Conditions of Hypofunction of the Suprarenal Apparatus

### 1. Addison's Disease.

**Definition.**—In the year 1855 *Thomas Addison* described the disease that bears his name. *The disease mostly develops in the third or fourth decades of life, usually quite insidiously, with adynamia and apathy. To these are added disturbances of the digestive tract (constipation, often alternating with diarrheas) and pigmenting of the skin and the mucous membranes; the patients succumb under a gradually increasing cachexia, not rarely with stormy terminal manifestations; autopsy almost always shows disease of both suprarenals, mostly tuberculous caseation. Addison's* description embraces all essential features.

**Symptomatology.**—The disease affects mostly individuals, not rarely hereditarily inclined to tuberculosis, who have been weakly from youth. Mostly it is individuals of middle age who are affected, rarely are children or old people affected. Almost always the disease manifests itself in ready fatigability, disinclination for work, and apathy; to these symptoms are sometimes added headaches, bad sleep, sometimes obstinate insomnia, psychical ill-humor and depression, often too, abnormal irritability; further, diminution in memory, noises in the ears, vertigo and commonly fainting attacks, singultus, and rheumatoid pains in the back and in the extremities, sometimes also epileptiform convulsions. Extremely stormy manifestations on the part of the nervous system may, especially in the later stages, make their appearance; violent delirium, acute confusion, convulsions, deep stupor, and coma. The symptoms on the part of the digestive tract are very various. The patients complain about pressure in the stomach, eructation, nausea, pyrosis, sometimes vomiting and epigastric pains. In the later stages there are mostly lessening or absence of the hydrochloric acid and ferment production. Often diarrheas alternate with constipation. The diarrheas may occur in crises with great violence, may be associated with spasms of the calves and simulate the picture in cholera nostras. In the terminal stages there are often immitigable vomiting. To this may be added abdominal pains and constipation; the abdomen is retracted, the abdominal walls are tense, the pulse becomes small and there exists in total the picture of peritonitis (*Ebstein*).

In the later stages the adynamia becomes prominent. Early the pulse is strikingly small and soft, the blood-pressure reduced, the force of the pulse lowered (*Münzer*). Dyspnea ensues on slight physical exertion. Edema is almost never observed, even later. Arteriosclerosis is extremely rare; when it is present, the rise in blood-pressure is wanting.

The blood picture always shows changes. The count of erythrocytes and the hemoglobin contents are almost always reduced, the leucocyte count is mostly normal. Lymphocytosis was first observed by *v. Neusser*. In the cases from the literature in which the leucocytic formula is given, especially in the cases of *Bittorf* and *Münzer* and in those described by myself, there was always present lymphocytosis. Hypereosinophilia is not constant. Moreover the large mononuclear cells are often increased, and the neutrophilic cells relatively and absolutely strongly diminished, sometimes to 40 per cent. Commonly there are found in addition signs of a status lymphaticus; swelling of the glands, the tonsils, the papillæ at the base of the tongue, etc. Also hyperplasia of the thymus was observed in some cases (*Weisel*, *Kahn*, *Hedinger*).

Of alterations of the metabolism should be mentioned especially the falling off in weight. In very rare cases only is observed corpulency lasting until death (*Bittorf*). Investigations as to the fundamental exchange are not known to me. The gastrointestinal disturbances are very well the cause of the emaciation. The few investigations as to the albumin metabolism are too short as to time. *Wolf* and *Thacher* found the endogenous uric acid elimination very low. In three cases of Addison's disease, *Eppinger*, *Rudinger*, and *I* found very high tolerance for grape-sugar and absence of glycosuria after injection of adrenalin. Also in a case of *Pollack's* was there no sugar after 2 mg. adrenalin. Later *O. Porges* found pronounced hypoglycemia (up to 0.033 per cent.) while in other cachexias the blood-sugar picture lay normally high. The finding of *Porges* that was corroborated by *Bernstein* in several cases, has therefore come to have a diagnostic value attached to it. The body temperature is often reduced, but when the manifestations become violent there may be found sudden increases in temperature, even to hyperpyretic values.

The making use of the diet is, so far as there are no diarrheas, normal; frequently there is indicanuria. In the later stages are found very frequently disturbances of the genital function, deficiency or absence of menstruation, in men diminution or loss of sexual power.

The *pigmentations* that are so important from a diagnostic point of view mostly begin on the uncovered parts of the body, or on parts where the clothing presses, or on parts on which certain irritants, for instance plaster, have exerted their action. Sites of especial predilection are the borders of the lids, the areolæ of the nipples, the linea alba, the genitalia, the anal folds, the folds of the palm; otherwise the palms, the soles and the nail beds usually remain free. In many cases too the hairs become darker. The pigmented places are light brown to dark brown, and in many cases the entire body may assume a bronze tint. Pigment displacements are less frequent. The pigmentations of the mucous membranes are almost always spot-like and blackish-blue in color. They are found on the borders of the lips, on the mucous membranes of the cheeks, on the soft palate and on the border of the tongue. Pigmentations of the vaginal and rectal mucous membranes are also observed. The skin pigment lies in the deeper layers of the rete Malpighii and is iron-free. In rare cases there is observed also a combination of Addison's disease with hemochromatosis (*Foà*, *Bittorf*, and *others*). The pigmentation is extraordinarily frequent. In the statistics of *Lewin*, based on five hundred sixty-one autopsied cases, it was found in 72 per cent., and *Bittorf* believes that these figures are too low.

The **course** of Addison's disease is very manifold. There are peracute cases in which destruction of suprarenal is brought about by hemorrhages, thrombosis, etc.; in these cases death may occur in a few days with stormy cerebral and intestinal manifestations. Pigmentation is absent.

A short time ago *Brodnitz* reported an interesting case which I shall repeat in detail. It was that of a thirty-six-year-old, strongly built, markedly fat man, previously healthy. Two and four years ago there suddenly occurred violent intestinal colics, that ceased after a few hours, and were followed only by a marked loss of strength. Also at present such a colic has come on quite suddenly. The facial expression is anxious, the pulse hard and full, 50–60 beats per minute, the temperature normal or slightly subnormal. No improvement on injection of morphine. This condition lasted two days and was then followed by an operation. On the jejunum and ileum were found columnar contractions of 10–20 cm. of the intestine at three places. Otherwise conditions were normal. In the course of the fourth day manifestations of peritonitis made their appearance. Tympanites appeared, the pulse was soft, thread-like, very rapid. Vomiting, temperature increased to 39° C. Death on the fifth day. At autopsy was found marked inflation of the stomach and duodenum, the small intestines and the colon. No peritonitis. Complete destruction of the right suprarenal, partial destruction of the left. On microscopical examination the left suprarenal at one place showed marked development of the connective tissue, with hemorrhagic pigment, in brief signs of a previous hemorrhage.

As a further example I cite the case of *Karakascheff*. A young man of eighteen years became sick suddenly with pains in the head and abdomen and felt very ill, but nevertheless went about. The manifestations became stronger only after three days, when vomiting ensued, and finally loss of consciousness. Autopsy showed old total destruction of the right suprarenal, apparently through thrombosis and a quite fresh infarction of the left suprarenal. Death had occurred five days after the beginning of the illness.

In other cases the affection lasts for weeks. Here the adynamia comes more in the foreground. In the case of *Straub* there developed within two weeks asthenia, adynamia, pigmentations that were iron-free, and only a slight depression of the blood-pressure. Also psychic disturbances (at first more excitement, then apathy) made their appearance. Autopsy showed a scirrhous carcinoma of the pylorus with metastases into the retroperitoneal tissue, especially at the hilus of the left kidney, into the lungs and pleura, and bilateral thrombosis of the suprarenal. The older of these could very well have occurred simultaneous with the beginning of the Addison's disease.

Moreover, sometimes in the subacute cases there is observed graded [schubweises] occurrence of the stormy manifestations. Chronic Addison's disease mostly shows remissions, in which also the pigmentation may retrogress. Cases that have lasted ten years are on record. As the remissions may have lasted for years, we must be cautious as to our assertions that an individual case has been cured.

Such individuals with chronic Addison's disease are for the most part very labile; physical exertion, excitements or slight complicating affections may lead to a fatal collapse.

As an example of the chronic course, I cite the following case:

*Observation XLVI.*—H. K., forty-two years. Entered the clinic Nov., 1911. No tuberculous taint; the family, however, shows the presence of gout. The illness began ten years ago, when a gradually increasing brown coloration of the skin became apparent; during the first years the coloration was extraordinarily intense, the greater part of the skin, but especially that of the face, the neck, hands and forearms being deep brown—a bronze color. Since that time the brown coloration has persisted in varying intensity. At that time the patient spent a year at Davos, as the lungs had become affected. Ten years ago an attack of articular rheumatism that affected especially the joints of the feet and toes. Since that time several attacks, two or three times a year, in which the most different joints are involved. At present such an attack is in progress after an interval of some years. Loss of 12 kg. weight during the last half year.

On examination, it was found that the skin of the whole body shows a brown coloration, which is especially intense on the extensor surface of the forearm, on the backs of the hands, on the face and neck, and on the genitalia and inguinal region. The brown coloration is partly diffuse, partly more circumscribed in spots, the individual spots attaining the size of a lentil. Mucous membranes of the lips, mouth and throat show numerous mustard-seed-sized, irregularly limited brownish-black spots, which are especially distinct on the mucous membrane of the cheeks. The mucous membranes are pale, the skin is dry, the percussion sound over the left pulmonary apex is shortened, the vesicular murmur weakened; no râles. The cardiac dulness is rather small, the heart-sounds are clear, the blood-pressure, according to *Gärtner*, 60, liver and spleen not enlarged.

Several joints are reddened, swollen and painful, especially both knee-joints, right great toe-joint, left ankle-joint, left shoulder-joint, right elbow-joint and left hand-joint.

No uric acid demonstrable in blood.

Traces only of albumin in the urine.

Temperature up to over 38°.

Estimation of sugar in the blood (*Bernstein*) 0.067 per cent.

Leucocyte count normal (8 per cent. eosinophiles). We are here dealing with the chronic Addison's disease, that has existed for ten years and that shows long remissions. During the last years the condition is apparently rather stationary, lately a new exacerbation (reduction in weight). With this there exists complications with frequently recurring articular rheumatism.

**Pathological Anatomy.**—Congenital errors of development of the suprarenal are often found combined with other malformations. *Zander* quotes forty-two cases of hemicephaly in which the suprarenals were always small. This finding is also constant with other malformations, if there is an absence of the anterior cerebral hemispheres. There apparently exists in such cases aplasia of the cortical system. At least *Elliott* and *Armour* in a case of anencephalus found the suprarenal medulla and the paraganglia normal, while the cortex was entirely absent. *Czerney* found the medullary substance entirely absent in five cases of congenital hydrocephalus. *Ulrich* observed in an adult complete aplasia of the suprarenal medulla; here the paraganglia must have been especially well developed.

Important practically is the hypoplasia of the chromaffin tissue described by *Wiesel*, *Hedinger*, *Goldzieher*, and *others*, which is mostly associated with status lymphaticus and sometimes with great parenchymal value of the thymus gland. According to *Wiesel* such individuals are especially predisposed to Addison's disease. Acute destruction of the suprarenals may occur as a result of hemorrhage of thrombosis of the suprarenal veins (*Virchow*, *Carrington*, *Karakascheff*, *Goldzieher* and *others* [*Lavenson*, *Hektoen*, *Ellis*]) or through suppuration (*Janowsky*). Much more frequent are simple atrophy or sclerosis (*Roloff*, *Simmonds*, *Bittorf*, *Goldzieher*).

*Bittorf* collected forty-seven cases of true atrophy or cirrhosis of the suprarenal glands, adding to these three cases of his own. In such cases the suprarenals are much decreased in size or entirely shrunken and often grown together with the surrounding tissue. Microscopical examination usually shows a very considerable reduction of the parenchyma, fattening and eventually necrosis of the cells. With the cirrhosis, one finds thickening or obliteration of the vessels, and growing together with the surroundings. Sometimes the sclerosis exists on a luetic basis (*Schwyzer*, *Esser*). *Esser* found gummata in connection with symptoms resembling Addison's disease in a new-born. According to *Lichtwitz*, pigmentations occur in all these cases. This author found the condition complicated with scleroderma in four cases in the literature, adding a fifth case. Most commonly, however, *tuberculosis* of the suprarenals is found bilateral, not rarely isolated. Often, however, other tuberculous foci in the body are found. Among five hundred forty-nine cases from the literature, *Elsässer* found isolated tuberculosis of the suprarenals in 17 per cent., in 48 per cent. combination with pulmonary tuberculosis, and tuberculous foci in other parts of the body in the rest of the cases.

In four hundred seventy-two cases the lesion of the suprarenal was bilateral. The suprarenals may be destroyed also by tumors. *Bittorf* reports two cases of hypernephromata with symptoms of Addison's disease.

There are also cases of Addison's disease in which the suprarenals are found to be healthy. *Nieszkowski* and *Virchow* first reported such cases. *Lewin* found them in 12 per cent. of five hundred sixty-one cases. There are, further, cases in which clinically no signs of Addison's disease are present, but at autopsy show destruction of both suprarenals. *v. Neusser* hence expressed the thought that a lesion in the splanchnic itself or at some other point of the sympathetic system could lead to Addison's disease. There are but few cases, however (*Jürgens*, *Bramwell*), that are adapted for such an explanation; otherwise changes in the sympathetic are rare and mostly slight (*v. Kahlden*, *Martineau*). An explanation of the above-mentioned exceptions would be possible only on the recognition that the suprarenals represent only a part of the chromaffin or interrenal system, and on the consideration of the presence of accessory suprarenals.

Whether the complete or partial destruction of the suprarenals will in a given case lead to Addison's disease, depends upon the fact whether the portion of the suprarenal apparatus lying outside the glands proper is sufficiently well developed to assume the function of the destroyed tissue, apparently also on whether the destruction has progressed slowly enough to give time for vicarious hypertrophy.

There has taken place a lively discussion as to whether Addison's disease should be referred to a lesion of the chromaffin tissue or the interrenal system. *Wiesel* in five cases of Addison's disease observed that the entire chromaffin tissue was destroyed, while the cortex seemed to be less affected. He thought that the destructive process began primarily in the chromaffin tissue, and involved the cortex only secondarily. On the other hand, *Karakascheff* reported cases in which chiefly the cortex was affected, and in which he regarded the cortical lesion as the sole course of the symptom-complex. The question is not as yet fully cleared up, although the pathologico-anatomical investigations of latter times and the physiological researches tend to vary more to show that in Addison's disease a *disturbance of function of both suprarenal systems* is present, a standpoint that is upheld in the new monographs (*Bittorf*, *v. Neusser* and *Wiesel*, *Biedl*). Of other pathologico-anatomical findings I mention only the known atrophy of the heart, and the atrophy of the sexual glands that is almost regularly present. *Kyrle* has made exact investigations as to the testicles. He found a deficient spermatogenesis and also changes in the interstitial glands.

It is very noteworthy that the suprarenal often becomes affected especially in severely infectious diseases and intoxications. Diphtheria toxin has an especial affinity for the suprarenals. In animals after the injection of diphtheria toxin, the suprarenals are always found to be markedly hyperemic and suffused with hemorrhages (*Roux* and *Yersin*). Necroses, hemorrhages, and edema of the suprarenals are found in the various infectious diseases (*Oppenheim* and *Loeper*). In many cases, an acute insufficiency of the suprarenal apparatus and especially the chromaffin tissue is well an important cause of the cardiac insufficiency. In such cases the suprarenals show an essential reduction in their adrenalin content (*Comessati*, *Schmorl*, *Goldzieher*).

Finally we must mention a rare finding of *v. Recklinghausen's*. In an eighteen-year-old dwarf who died in convulsions, he found what was apparently a very chronic tuberculous change of both suprarenals. I shall have occasion to refer to this case later.

**Pathological Physiology of the Suprarenals.**—The thesis established by *Brown-Séquard* that the extirpation of both suprarenals led to the death of the animal experimented on has met with much contradiction. The sure knowledge that the cortical system and chromaffin tissue are in like manner important for life was first mentioned by later investigators (I mention only *Biedl*, *Hultgren*, and *Anderson*) who took into consideration the presence of accessory suprarenals.

*Biedl* could at the same time furnish important demonstration that the death of the animal was not to be blamed on the operative shock due to injury of the sympathetic nerve plexus, as the operation also ended fatally after transplantation of the suprarenals under the skin. After extirpation of both suprarenals, the animals, after a latent period, showed increasing apathy, adynamia, paresis, and emaciation. Blood-pressure and bodily temperature gradually sank, as did also the amount of blood sugar (*Porges*, *Bierri*, and *Malloisel*). Injection of phloridzin would now produce no glycosuria or only minimal glycosuria (*Eppinger*, *Falta*, and *Rudinger*); the glycogen rapidly disappeared from the liver and muscles (*Porges*), there existed a higher sensitivity for poisons (*O. Schwarz*), the blood seemed to act·toxic, death occurring in convulsions. The symptom picture shows great similarity with the peracute case of Addison's disease. We have not as yet a sufficient explanation as to the question as to which symptoms of Addison's disease are to be referred to the absence of the medullary system and which to that of the cortical system. Before I enter into this question, I will briefly mention the most important facts we know as to the physiological significance of these systems.

The active constituent of the chromaffin tissue is adrenalin. After the important preliminary researches of *v. Fürth*, it was first isolated in a crystalline form by *Takamine* and *Aldrich*.

Later investigations of *Aldrich*, *v. Fürth*, *Pauli*, *et al.* then led to the establishment of its chemical formula. It is a methylaminoethanol pyrocatechin and has the formula $C_9H_{13}NO_3$.

*Stolz* first succeeded in making optically inactive adrenalin synthetically, and *Flächer* then obtained the separation into the dextro- and sinistro-adrenalins. The sinistro-adrenalin is far the more active and is identical with that produced in the body (*Abderhalden*). Probably the organism forms adrenalin from the aromatic split products of albumin, tyrosin, and phenylalanin or oxyphenylserin (*Halle*, *Fränkel*, *Friedmann*).

Of the chemical methods for demonstrating adrenalin we will mention only the iron chloride test (*Vulpian*), the sublimate test (*Comesatti*), the iodine reaction (*Vulpian*, *Schur*, *Fränkel*, and *Allers*), the potassium permanganate lactic acid test (*Zanfrognini*).

I shall limit myself to sketching briefly the most important of adrenalin's physiological actions. It acts as a powerful increaser of the blood-pressure through narrowing of the peripheral vessels, it mostly acts first by slowing the pulse, then accelerating the pulse; it slows the pulse by reflex excitation of the vagus center, this action belonging to the so-called by-activities [Nebeneinwirkungen] of adrenalin (*Biedl*). Other by-activities are the shallowing of respiration, and, according to *Biedl* perhaps also the increase of the excitability of the striated muscles. It acts in a relaxing manner on the stomach and intestines, as a contracting agent on the three sphincters (the pyloric, the ileo-colic, and the internal sphincter of the anus). The uterine muscle is contracted or relaxed by adrenalin, according to whether the pressor [fördernden] or the inhibitory fibers predominate or are excitable (*Falta* and *Fleming*). Probably the bladder behaves in the same manner. Under circumstances mydriasis occurs. The vessels of the kidneys react to minimal doses by dilatation and diuresis (*Jonescu*). Under circumstances adrenalin may produce salivation and secretion of tears, indeed in large doses (in guinea-pigs), also secretion of sweat (*Falta* and *Ivcovič*). Adrenalin produces hyperglycemia and glycosuria (*F. Blum*, *Metzger* and *Zültzer*). The hyperglycemia comes about by mobilization of the glycogen and probably also by secondarily increased carbohydrate formation in the liver (*Eppinger*, *Falta*, and *Rudinger*, *L. Pollak*). It increases the albumin decomposition during hunger. At the same time the respiratory quotient is temporarily increased (*Bernstein* and *Falta*). In large doses it produces in dogs increased elimination of uric acid and allantoin. Often it leads to increase of temperature. Further it brings about a neutrophilic hyperleucocytosis, during which the eosinophiles vanish from the circulating blood. The simultaneous increase of the mononuclear cells is a by-action, as this remains absent after the administration of atropine. Finally adrenalin produces hyperglobulia (*Bertelli*, *Falta*, and *Schweeger*), chiefly through transudation of plasma.

Apart from the accessory actions mentioned, adrenalin acts only on the purely sympathetic nerve-endings, and indeed on the so-called musculoneural junction (*Langley*, *Elliott*). It is therefore a purely sympathetic hormone. The giving-off of adrenalin to the blood of the vena cava is continuous. The blood of the suprarenal vein should contain about one-half part per million of adrenalin per cc. (*Ehrmann*). *Biedl* estimates that in twenty-four hours about 4.3 mg. are given off to the blood. This amount of adrenalin may be increased by stimulation of the suprarenal nerves (*Biedl, Asher*).

The assumption that the activity of the chromaffin tissue and the excitability of the myoneural junction (*Bayliss* and *Starling*) is regulated by centers lying in the medulla oblongata is essentially based on the knowledge that "puncture glycosuria" is brought about by dissemination of adrenalin by means of chromaffin tissue. Already *Blum* had supposed this. *Eppinger, Falta*, and *Rudinger* further pointed out concerning this that in the dog without a thyroid, "piqûre" may remain as ineffective as injection of adrenalin. After *A. Mayer* had established the fact that "piqûre" remains ineffective in rabbits after bilateral removal of the suprarenals, *Waterman* and *Smith* tried to demonstrate an adrenalinemia by means of the insufficient *Ehrmann's* reaction. The question was first entirely cleared up by the investigations of *R. Kahn*. This author could show that after the sugar-puncture, the tingibility of the suprarenals to chrome stains in great part disappears and the contents of adrenalin markedly diminish. Cutting of the splanchnic nerves not only prevents the occurrence of "piqûre" glycosuria, as *Claude Bernard* had shown, but also the coming about of any change in the suprarenal medulla. It should be noted that in rabbits the right suprarenal is supplied by the right and left splanchnic, the left by the right splanchnic only.

We will now consider the path that adrenalin takes in the body. The blood in the cava, containing the adrenalin, first reaches the right heart and then the lungs. The pulmonary vessels act refractory to it; hardly any adrenalin is consumed here (*Brodie* and *Dixon*). From the lungs it reaches the left heart and from this the greater circulation. The coronary vessels of both sides of the heart are dilated by it, hence the heart is better permeated with blood (*Langendorf*). That part of the adrenalin-containing blood which flows through the brain, also hardly loses in its adrenalin contents; the cerebral vessels are dilated (*Gerhardt*). On the contrary there occurs a marked consumption of adrenalin in the other peripheral capillary territories of the body, especially the muscles and the intestines (*Elliott, Carnot*, and *Josserand, Falta* and *Priestley*). It therefore is to be assumed that the blood proceeding from these organs (veins of the extremities, portal veins) is adrenalin-free or at least poor in adrenalin. Therefore it is very striking that the test of the arterial and venous blood as to its adrenalin contents by means of the known biological methods (frog eyes, strips of vessel, uterus method) in the experiment of *Falta* and *Fleming* showed just as strong an action, if indeed not stronger, of the venous blood (extremity). On the contrary, after the subcutaneous injection of adrenalin, the arterial blood showed stronger action. We must therefore be very cautious in the interpretation of the biological methods mentioned, as the pressor action of the blood serum must depend on other, as yet unknown, factors, a view that is also upheld by *O. Connor*. I shall have something to say later as to the value of the biological methods that we use for demonstrating adrenalin in the blood serum. However this may be, a stronger unloading of the chromaffin tissue must lead to a quite definite distribution of blood. We find slight hyperemia of the lungs, the heart, the brain, the kidneys, marked hyperemia of the peripheral venous system and before all that of the liver and the roots of the portal vein, while the other capillary systems are poor in blood. The purpose of this arrangement is evident. It means the forcing of a greater amount of blood into those organs which are the seat of life-maintaining centers and of the regulation of metabolism, thus heightening the activity of these organs. The liver occupies an especial position: It receives adrenalin-poor or adrenalin-free blood through the portal vein and thus becomes markedly hyperemic, and blood containing adrenalin through the hepatic arteries; it seems that by this means especially favorable conditions are provided for the action of adrenalin on the metabolism (*Falta* and *Priestley*). Also *E. Neubauer* found by oncometric methods a hyperemia of the liver after the injection of adrenalin.

The physiological significance of the chromaffin tissue may be adduced from what has just been said with regard to adrenalin's intensive and manifold actions. We may assume that it maintains the normal excitability of the sympathetic nerves and that by means of graduation of the secretion it is concerned in the regulation of the blood-pressure, the distribution of blood, and the tonus of all other organs innervated by the sympathetic; further that it maintains constant the amount of sugar in the blood and enters in a regulatory manner into other factors of the metabolism; further that it influences muscular power (whether directly or through carbohydrate metabolism is questionable); and finally it exercises an influence on the production of neutrophilic leucocytes and on the plasma contents of the circulating blood.

As to the function of the cortical system, we as yet know very little. According to *Jacoby*, it contains an oxydase. *Lohmann* obtained cholin from the cortex. Cholin acts as a toning agent on the autonomous nerves and it is also found, however, in many other organs, and we do not know whether it is given off from the cortical system in the blood paths. The assumption of a "système cholinogene" (*Gautrelet*) as an antagonistic regulator against the chromaffin system has not as yet received sufficient support. Also the experiments of *Goldzieher* do not seem to me conclusive enough with respect to the significance of this question.

It is assumed rather generally that the cortical system possesses a detoxicating function (*Brown-Séquard*). The blood of animals without their suprarenals seems to be poisonous. As has been mentioned previously these animals show a greater susceptibility for certain poisons; this does not, however, furnish absolute evidence for the detoxicating activity of the suprarenals, as we may assume with *Theiroloix* that the withdrawal of the regulatory function lessens the general resistance. It is supposed by many authors that the symptoms on the part of the intestinal tract and the central nervous system, which are severe and remind one of an acute poisoning, depend on the falling out of the function of the cortex. It should further be mentioned that in the growing organism enormous influences on sexual glands and the general hairiness proceed from the cortical system. I shall come back to these in detail later.

**Pathogenesis of Addison's Disease.**—Also the results of the pathologico-physiological investigations just cited justify the dictum *that Addison's disease depends on an acute or chronic more or less complete loss of the function of the suprarenal apparatus.*

Probably from youth up there exists in individuals who acquire an Addison's disease a certain weakness of the suprarenal function (*Wiesel*). Almost always we find pathological processes which have affected the suprarenal apparatus itself, but we cannot on this account rule out the assumption that an affection of the nervous apparatus regulating the activity of the suprarenal apparatus cannot lead to a (after a fashion) purely functional Addison's disease.

Very difficult is the comprehension of the rare cases of Addison's disease with unilateral affection of the suprarenal apparatus that become healed after extirpation of the affected suprarenal. *v. Neusser* has supposed a reflex influencing of the healthy suprarenal after the manner of reflex anuria, and *Bittorf* a damaging of the same through abnormal metabolic products of the diseased gland.

Among the symptoms of Addison's disease depending on the lessening of function of the chromaffin tissue probably are the low blood-pressure, the low sugar contents of the blood, the abnormally high tolerance for grape-sugar, the adynamia, and the mononucleosis or the status lymphaticus, although in the explanation of the alterations in the hematopoetic apparatus we must not forget what is frequently present—tuberculosis. To the deficiency of the cortical system are referred by most authors the manifestations on the part of the gastrointestinal tract, vomiting, diarrheas, etc., and the psychical alterations, the convulsions, delirium, coma, etc. No certain justification for these views have as yet been adduced (see later).

Very difficult is the interpretation of the coming into existence of the *pigmentations* in Addison's disease. The pigment is always iron-free. On reduction with hydriodic acid it yields no hemopyrrol and on oxidation no hematinic acid. We have, therefore, discarded any relationship with blood pigment, and have found the mother substances in the aromatic split products of albumin (tryptophan, tyrosin, and also adrenalin) (*S. Fränkel*). Further, *Zülzer* and *Lichtwitz* saw the occurrence of pigmentation of the skin and mucous membranes after the injection of adrenalin in rabbits. As according to *Eppinger* the melanogen in melanocarcinoma is an N-methypyrrolidinoxycarbonic acid and its elimination is increased through the administration of tryptophan, so it would not be unlikely that an increased production of tryptophan has been brought about in the body by the administration of adrenalin. Further it should be mentioned that *Neuberg* demonstrated in the tumors of the cases of melanoma of the suprarenal cortex a ferment which let a pigment formation be recognized after the addition of adrenalin or oxyphenylethylamin. Further *Jaeger* has obtained from a melanoma an enzyme that decomposes adrenalin with pigment formation. *Jaeger* supposes that adrenalin is the mother substance of the iron-free pigment of the organism. Finally, according to *Meirowsky*, freshly excised pieces of skin show in the incubator an increase of pigmentation, and according to *Königstein* this increase of pigment is greater in the skin of dogs without their suprarenals. Therefore it would not be unlikely that the cortex as well as the chromaffin takes part in the pigment formation, the first furnishing the mother substance of the melanogen (tryptophan), the latter the further decomposition. Increased formation of pigment may occur under the most diverse circumstances, as in Basedow's disease, when the production of adrenalin is increased, or in Addison's disease when the production of adrenalin is absolutely lessened, or perhaps less disturbed than the function of the cortical system. Thus may also be seen why pigment formation often remains away entirely in acute destruction of the entire suprarenal apparatus. This should, however, be regarded merely as a hypothesis that still requires experimental support.

**Differential Diagnosis.**—For differential diagnosis of great importance are the pigmentations. The number of cases of Addison's disease without melanoderma is, as *Bittorf* has emphasized, less than the older statistics would lead one to expect. Similar pigmentations are found, however, in normal individuals. Also in itching skin affections and [those due] to vermin, during the use of arsenic, in pregnancy, in chronic heart affections and in phthisis pulmonalis; in slight grades of the latter the thought of Addison's disease may be erroneously awakened on account of the emaciation and the slighter hypotonia; it is hence important to remember that in all conditions enumerated the mucous membranes remain free. In persons cachectically tuberculous the pigmentations may become quite similar to those of Addison's disease. Here indeed is it questionable whether the pigmentations might not be referred directly to a damaging of the suprarenal function, an opinion that is upheld by *Lavignel-Lavastine.*

In cirrhose bronzée the coloration of the skin is more blue-gray; here also, the mucous membranes are affected only rarely and more in a diffuse form (*Heller*). Here we should consider the liver lesion and the eventual complication with pancreatic disease (diabetes). Naturally it should be taken into consideration that combinations of cirrhose bronzée and Addison's disease may occur, if the sclerosing process in cirrhose bronzée also involves in strong degree the suprarenal apparatus (*Foà, Bittorf*). As is known, pigmentations are also frequent in scleroderma. From this we must not conclude that a complication of scleroderma with Addison's disease is present in the individual cases as pigmentations belong to scleroderma as such. Also similar pigmentations are observed in pellagra (*v. Neusser*). Statements as to the characteristic erythema in the warm seasons of the year clinch the diagnosis in this case. Arsenic melanosis and argyrosis show another tint. Pigmentations are also observed in leucemia. *v. Neusser* thought that there were leucemic infiltrations of the suprarenals, which opinion was later corroborated, in a case by *Ziegler*. Pigmentations in Basedow's disease are very common. The complication with Addison's disease is very rare. However, such cases in which the diagnosis was confirmed by autopsy have been reported by *Fletscher* and *Greenhow*. Such a diagnosis should be made in vivo with great caution, as markedly pigmented cases of Basedow's disease with cachectic symptoms—such as occur in the latter stages—can easily give rise to the impression of a concomitant Addison's disease.

Very difficult is the delimitation from cachectic conditions associated with occult carcinomas and diseases of the liver, in which diseases melanoplakia of the oral mucous membrane may occur also (*Schultze*). In these cases and in the case of Addisonoid anemias described by *Grawitz*, the demonstration of a hypoglycemia and of a mononucleosis with hypereosinophilia is very important.

The diagnosis of acute Addison's disease may be very difficult. *Brodnitz* points out the importance of the following syndrome: Extraordinary slowing of the fully tense pulse with normal temperature; violent intestinal colics occurring in attacks; failure of the peristalsis and isolated intestinal distention. *Brodnitz* believes that thrombosis of the suprarenal vein occurs in many cases of postoperative spastic occlusion of the intestine.

The **prognosis** of Addison's disease is always very dubious. The few certain cases of cure concern mostly luetic disease of the suprarenal, some with and some without specific treatment (*Merckel* and *Birch-Hirschfeld*); in a case of *Oesterreich's* the extirpation of the one tuberculous suprarenal led to cure. Cure has also been observed in cases of hypernephroma with Addisonian manifestations (*Bittorf*).

**Treatment.**—It remains to be said that treatment is very ineffective. The statements as to improvement after subcutaneous or peroral administration of suprarenal substance are more sparse than those concerning results that are negative. The administration of small doses of adrenalin per os is ineffective, as might be gathered from our researches, which show that even more than 20 mg. per day do not call forth any especial manifestations. Only when the doses are very much larger did we see in animals after administration for days the occurrence of hyperglycemia (*Falta* and *Turin*). I quote one of our experiments:

8.3 kg. dog, Mar. 5, sugar in blood 0.1008 per cent.

On March 8, the dog received daily 25 cc. of a 1 per cent. solution of adrenalin through the stomach tube.

From March 9 to 16, inclusive, 25 cc. adrenalin twice.

Mar. 16, sugar in blood, 0.1552 per cent.

From Mar. 19 to 30, inclusive, 25 cm. adrenalin twice.

From Mar. 13 to 17, a trace of sugar was demonstrable in urine, later the urine was always sugar-free, but contained traces of albumin.

Subcutaneous injection of adrenalin is not advisable for any length of time. *Boinet* saw manifestations of collapse. Also after the injection of the glycerine extract of the whole suprarenal there occurred in *Boinet's* case, after a time, conditions of excitement, tremor, and insomnia. Perhaps, however, a slight result is to be obtained by the peroral administration of tablets made from the whole gland. According to *Magnus-Levy*, the pigmentations have become lighter in color after the administration of these tablets, under certain circumstances.

The beautiful investigations of *v. Haberer* and *Stoerck* as to the healing-in of pedunculated suprarenal glands [transplanted] into the kidney scarcely give hopes for a practical application, as apart from the necessary pedunculation, probably only autotransplantations of the suprarenals are possible.

Only the symptomatological treatment remains. *Grawitz* recommends washing the stomach with sodium chloride solution, predomination of vegetative diet, avoidance of alcohol, and hydrochloric acid medication. *Grawitz* saw a case that presented all the symptoms of Addison's disease which benefited under this treatment. Also the pigmentations of the skin disappeared. The case was observed for a period of three years after this successful result. Very important in Addison's disease is the avoidance of every severe exertion. *Boinet* reports seven cases of sudden death in Addison's disease, immediately after a marked fatigue.

Proceeding from the observation that dogs after the extirpation of their suprarenals, lose all their glycogen except traces, *O. Porges* combated the adynamia in several cases of Addison's disease by the administration of large amounts of carbohydrates (especially of levulose) with good results. Also *Gautrelet* reports favorable results.

Here might also be mentioned the *favorable results of adrenalin in other diseases. Very widespread is the employment* of adrenalin in the stilling of hemorrhage. Proceeding from the observation that animals bear enormous amounts of adrenalin, *Turin* and *I* in ulcus ventriculi increased administration of adrenalin per os up to 7 mg., thrice daily, and up to the present have seen good results. Many authors report the excellent action of adrenalin in condition of collapse (*John* and *others*), especially in the infectious diseases (for example, *Heubner*, in diphtheria). According to our observations adrenalin given subcutaneously, too, in man increases the blood-pressure, often for a long time. According to our experiment the subcutaneous injection is to be preferred in not too urgent cases.

Several times we saw, too, an astonishing result from subcutaneous administration (thrice 5 mg., each in one-fourth glass of water) in obstructing carcinoma of the esophagus, in which the passage was reestablished probably by subsidence of the tumefaction of the inflamed mucous membrane, but such results only last for a few days. Further, adrenalin was introduced by *Neu* into obstetrical practice. After the injection of adrenalin the uterus was brought to a condition of tetanoid contraction. The drug has been especially serviceable in Cesarean section. It may be injected either subcutaneously or directly into the uterus. Probably pituitrin will supplant adrenalin in this respect, as it has the same action and is less deleterious.

The employment of adrenalin is also useful in phosphorus poisoning. *E. Neubauer* and *Porges* observed that in animals poisoned with phosphorus, the stainability of the chromaffin tissue to chromic acid disappeared; both these authors attribute the vanishing of carbohydrates from the liver, the subsequent fattening of the liver and the hypoglycemia (*E. Neubauer*, and *Frank* and *Isaac*) to the falling out of the chromaffin tissue and in most cases could actually prevent these symptoms by the administration of adrenalin.

As to the treatment of osteomalacia with adrenalin, see chapter on sexual glands (appendix).

### 2. Isolated Symptoms due to Failure of Function of the Suprarenal Cortex

In the consideration of the pathogenesis of Addison's disease, it has been pointed out that we as yet know nothing certain concerning that group of cases which has as the basis of the symptom-complex the destruction of the suprarenal cortex. It is true that many authors regard the manifestations of intoxication that tend to enter into acute cases and in the terminal stages of Addison's disease as due to deficiency or absence of the suprarenal cortex. But as yet experimental pathology has furnished no certain foundation for this assumption. Also clinical observation, as will be seen from the following, does not seem to me to substantiate this assumption.

First let us consider the malformations. In anencephalus is found, as has already been mentioned, in addition to anomalies in the genital organs, also aplasia of the suprarenals. *Apert* points out that in aplasia of the suprarenals the cortical defect seems to play the most important rôle. I mention again the case of anencephalus reported by *Elliott* and *Armour*, in which the suprarenal medulla and the paraganglia were intact. Also in cases in which the suprarenals are entirely absent the paraganglia may be normal, as in the case of *Apert*. The aplasia of the cortex in the new-born is the more remarkable because here the suprarenals, as is known, are especially well developed.

An indication as to the direction in which are to be found manifestations of deficiency of the suprarenal cortex is found, under certain circumstances, in adenomata of the suprarenal cortex. We shall see later that in such hyperplasia of the cortex there occurs in youth abnormally rapid growth of the organism and premature development of the secondary sexual characters and the genitalia, and in adults a tendency to abnormal hairiness. Hence arises the thought that when manifestations of the opposite kind are present there may exist a cortical insufficiency.

Moreover, in the chapter on the hypophysis I have reported a case of hypophysial dystrophy in which the disease first developed in later life and led to a marked retrogression of the hairiness on the trunk and on the face. In this case both suprarenals were found to be highly sclerosed and we shall see later in the consideration of the multiple *ductless glandular sclerosis* that in man a retrogression of the secondary sexual characters may indeed set in as the result of the failure of the function of the sexual glands, but that in woman the mere loss of the function of the sexual glands is not usually followed by distinct retrogression. First in cases in which the sclerosing process involves numerous ductless glands does there seem to be in women a distinct, and in men a marked retrogression of the hairiness and the genital organs.

In the cases of multiple ductless glandular sclerosis in which there have been autopsies there is always to be found a marked sclerosis of the suprarenal cortex. Further there should be observed in eunuchoidism whether in rare cases there does not exist, in addition to the hypoplasia of the sexual glands, a hypoplasia of the suprarenal cortex.

Finally *Variot* and *Pironneau* have described a case which was characterized by marked disturbance in growth, absence of any hairiness at all (eyebrows, lashes, and almost complete baldness of the head). They have designated this case "nanisme type senile" and refer to two entirely analogous observations by *Gilford Hastings* and *Sir* [*Jonathan*] *Hutchinson*. In the last case the suprarenals were found to be sclerosed. *Variot* therefore concludes that these vegetative disturbances depend on a loss of the function of the suprarenal cortex. It seems to me, however, that in the case of *Hutchinson* there was an insufficient examination of the other ductless glands. Also *Gilford Hastings* points this out, and I hold that it is not impossible that this case constitutes multiple ductless glandular sclerosis in childhood, although I am not in a position to prove this. Perhaps some objections may be made against this view. At least I shall speak again of these cases under the consideration of multiple ductless glandular sclerosis.

It is also doubtful whether the dwarf described by *v. Recklinghausen* should be grouped under cortical insufficiency. In a dwarf eighteen years old who had died in convulsions, *v. Recklinghausen* found an apparently chronic tuberculous caseation of both suprarenals. The individual was 95 cm. tall and 10½ kilos in weight. The measurements correspond to about that of a three- or four-year-old child. The bodily dimensions were well proportioned. The epiphysial junctures were retained, the penis and the testicles were rather small. If we were already disposed to regard a loss of the suprarenal function as the cause of the disturbance in growth, we would have to hold responsible the suprarenal cortex, as hypoplasia of the chromaffin tissue rather produces a tall, weak, individual. I regard as more likely that here we are dealing with a true dwarfism and that the suprarenal caseation constitutes an accidental complication.

If again we review the preceding material, we find that it is a question if the observations are to be referred to an isolated withdrawal of the cortical function. The observations seem rather to suggest that from the cortex there proceeds a furthering influence on the genital sphere and especially on the hairiness, an assumption, as we shall see later receives essential support through corresponding manifestations in hyperplastic conditions of the cortex. These observations furnish no support for the assumption that loss of the function of the suprarenal cortex leads to manifestations of intoxication.

## b. Conditions of Hyperfunction of the Suprarenal Apparatus

Here we are interested especially in tumors of the suprarenal apparatus, which usually, but not always, are associated with conditions of hyperfunction.

### 1. Tumors that Proceed from the Chromaffin Tissue

These seem to be very rare. *Küster* describes two cases of glioma of the suprarenals, one affecting a fourteen-month child whose entire right suprarenal had been converted into a tumor, while in the left suprarenal was found a tumor occupying the site of the medulla. Numerous metastases were present.

In the second case the findings were accidental. *Küster* regarded these tumors as a glioma, *Wiesel* as a growth made up of formative cells of the sympathetic, although *Schilder* has lately described a certain glioma of the sympathetic and regards Küster's case as glioma. More recently there have been described chromaffin tumors, in part too proceeding from the paraganglia, by *Weichselbaum*, *Manasse*, *Stangl*, *Mönckeberg* and *Kolisko*. *Kolisko's* case (reported by *v. Neusser* and *Wiesel*) was that of a vigorous otherwise healthy man who suddenly died during cocaine anesthetization on account of the extraction of a tooth. Here was found a bilateral suprarenal tumor made up of chromaffin tissue, and very rich in adrenalin. *v. Neusser* and *Wiesel* regard this case as adrenalin intoxication. Very interesting is the case of *Wiesel*, a tumor of the sympathetic in a two-year-old child with arteriosclerosis which resembled histologically the sclerosis produced experimentally in animals by adrenalin. Hence it seems that these tumors can be associated with hyperfunction of the chromaffin tissue. For this also speaks the frequently observed cardiac hypertrophy.

Moreover, there should be mentioned here the case of *Kawashima.* In this case were found multiple skin fibromata proceeding from the connective-tissue sheath of the nerves, and also tumors of the suprarenal medulla. *Kawashima* discusses the association of neurofibromata with diseases of the nervous system. He points out that neurofibromata are very frequently associated with general symptoms (disturbances of nutrition, intellectual disturbances, gastrointestinal affections, certain visual disturbances, headaches, spasms, depressed states, and alterations in the sexual sphere) and believes that these as well as the general symptoms are the expression of an affection of the nervous system. There should also be mentioned two cases of paraganglioma reported by *M. Herde.* Both cases were those of chromaffin tumors. In one case there existed arteriosclerosis, in the other genuine "Schrumpfniere." Finally I mention a case of *Sazuki's* (chromaffin tumor of the suprarenal medulla) and of *E. Hedinger's* (struma medullaris cystica suprarenalis).

The question as to whether there exist conditions of hyperfunction of the chromaffin otherwise than when due to tumor has been recently discussed. It is noteworthy that numerous authors take the negative attitude concerning this question, at least as far as chromaffin tissue is concerned. In tumors of the chromaffin tissue we have learned to know a group of clinical conditions, which we may regard as due, with great probability, to an increased function of the chromaffin tissue.

Are we then justified in regarding similar clinical conditions as the expression of a hyperfunction of the chromaffin tissue, even where a pathologico-anatomical substratum has not as yet been found for them?

Originally French authors (*Pilliet, Vagues, Aubertin* and *Ambard*) endeavored to explain the increase of blood-pressure in interstitial nephritis by an increase in the function of the suprarenal cortex, as they often met with strikingly large suprarenals in cases with hypertonia. *Josué* has assumed such in the atheromatosis associated with hypertonia. After, however, we had recognized the significance of the chromaffin tissue for the regulation of blood-pressure, *Beaujard* regarded it as regulative against increased circulation of toxic products in the organism, which would be conditioned on the lessened eliminatory capabilities of the kidney. Apparently the chromaffin tissue alone seems to be significant for the pathogenesis of this condition, in so far as we might wish to bring it into correlation with the suprarenal apparatus. The question should, however, be formulated as to whether secondary hyperfunctional conditions of the chromaffin tissue occur as the reaction to other processes in the body, processes that are released eventually by a permanent reflex condition of over-excitement of the centers of this system lying in the medulla oblongata or in the brain stem; also we should consider the possibility as we have discussed in Basedow's disease, that these centers are primarily in a state of hyperirritability on grounds that are not at all clear. In this case we could speak of a true neurosis.

*Wiesel* was the first who referred the disease process associated with hypertonia to a condition of hyperfunction of the chromaffin system. He found hyperplasia of the chromaffin tissue in twenty-two chronic and some acute cases of nephritis, and in a case of aortic insufficiency—all cases showed cardiac hypertrophy—the hyperplasia affected the suprarenal medulla as well as the paraganglia. Later *Schur* and *Wiesel* tried to demonstrate in such cases the increased amount of adrenalin in the blood, by means of the *Ehrmann-Meltzer* reaction. The hyperplasia of the chromaffin tissue was corroborated by numerous authors, of whom are named *Schmorl, Goldzieher*, and *Molnar* and *Comisatti*. *Schmorl* and *Goldzieher* also found an increase in the adrenalin content of the suprarenals. Other authors, as *Bittorf*, found no such hyperplasia. Certain negative cases do not seem to me to mean very much, as not every case of hyperplasia need be distinct. The statements as to the increased adrenalin content of the serum have met with more contradiction. It is certain—with the following my own experiences agree—that in numerous cases with hypertonia the frog's-eye method fails. But also other fine biological methods give negative results, for *Schlayen*, using *Meier's* vessel-strip method, and *A. Fränkel*, using the myographic method, found the serum of nephritics even less active than normal serum. These behaviors were complicated, as *Schlayer* ascertained, by the foreign serum in a manner that could not be overlooked. The myographic method is, however, from its very nature hard to interpret, for *Fleming* and *I* also on the use of an adrenalin-Ringer-solution, saw inhibition of the movements and the tonus of a rabbit's uterus. *O'Connor*, using the *Laewin-Trendelenburg* frog muscle method came to like results. He found that the activity of the serum was conditioned not only by its adrenalin content but also by other substances, that first get into the serum on coagulation. We therefore can say only that up to the present the biological methods do not furnish a certain evidence for the increased adrenalin content of the serum. On the strength of this, however, I do not feel justified in denying the teaching of *Schur* and *Wiesel*. In favor of it speaks in addition to the hyperplasia of the chromaffin tissue the increased diuresis, which agrees with the increased amount of sugar in the blood as shown by *E. Neubauer* and also, as I believe, with alterations in the distribution of the blood as seen in experimental hyperadrenalinemia. Very frequently we see congestive conditions in the lungs, in the brain (retinal hemorrhages, apoplexies), and in the liver. In beginning decompensation very often the swelling of the liver is the first to appear. Again, in such conditions, very often at the beginning, we see a slight grade of hyperglobulia; later the count of red blood cells is very often reduced (destructive effect of chronic adrenalinizing on the erythropoesis). Finally we find the count of neutrophilic cells mostly at the upper limits of the normal or even slightly exceeding these.

As to the question why interstitial nephritis is associated with an increase of function of the chromaffin tissue I shall not enter into here more intimately. In many cases, for instance, in the nephritis of scarlet fever, the disease of the kidney is primary, in other cases the contracted kidney can only be a partial manifestation of the general arteriosclerosis of the small blood-vessels. Such a general arteriosclerosis must lead reflexly to a hypertonia through lowering of the resistance, if the accessory amount of blood should be driven through the capillary system of the muscles, etc. Finally it is conceivable that the increase of function of chromaffin tissue (as for instance in tumors of the sympathetic, perhaps also in premature arteriosclerosis of diabetics, or in transition of diabetes into contracted kidney) is the primary factor (*Frank's* hypertonic diathesis).

Still less clear is the significance of the chromaffin tissue for the coming into existence of the atheromatosis. As is known, chronic adrenalizing of rabbits can produce sclerosis of the great vessels (*Josué*, *Erb*, and *others*). This is an affection of the media. The vascular lesions in tumors of the sympathetic are also affections of the media. *Braun*, however, by the intravenous injection of minimal doses of adrenalin could produce atheromatosis of the small vessels. The ordinary arteriosclerosis of the large vessels, that occurs without increase of blood-pressure, has nothing at all to do with the chromaffin tissue; it depends on a primary degeneration of the elastic elements.

Finally, some observations as to the *influence of hyperfunction of the chromaffin tissue on the carbohydrate metabolism.* In hypertonics we find, as already mentioned, hyperglycemia. The kidneys adapt themselves to a very gradual increasing amount of sugar in the blood, without glycosuria (*v. Noorden*). In many cases of diabetes mellitus, and especially in advanced cases, much speaks for the view that here also there is a slight overproduction of adrenalin (*Falta*, *Newburgh*, and *Nobel*). That the administration of this escapes detection by the known biological methods is not to be wondered at, when on the one hand we take into consideration the unreliability of the biological methods (see above) and on the other, consider what monstrous dilution, 1 gm. of adrenalin, which under circumstances may produce much sugar in the urine, must experience when injected subcutaneously in man. Such a slight increase in adrenalin production may very well be overshadowed by the counter-regulations without leading to increase in blood-pressure. On the contrary the toxic components seem to dissociate as is shown by the premature arteriosclerosis so frequently observed in diabetes. An exact histological study of the same has not as yet been made. Finally we should point out the frequent transition of diabetes into contracted kidney. On the grounds detailed the negative standpoint that *G. Bayer*, *Bröking* and *Trendelenberg* have taken against the assumption of a functional increase of the chromaffin tissue in certain forms of diabetes mellitus, does not seem to me a priori to be justified.

### 2. Tumors that Proceed from the Cortex

These appear to possess greater clinical interest than the tumors of the chromaffin tissue. The knowledge that they may be associated with hyperfunction of the cortical system is one of the achievements of recent years. In a clinical respect we can distinguish two groups of cortical tumors. In one of the groups belong chiefly the sarcomata, lymphosarcomata, carcinomata, alveolar sarcomata, endotheliomata, the melanotic carcinomata and the cysts (literature in *Bullock* and *Sequeira*, *Frew*, *Glynn*, *Tilestone*, *Winkler*, *Hanschen* and *Arnaud*). These seem to bring forth only the usual symptoms of a benign or malignant tumor. We shall not discuss this group any further. The other group embraces the numerous cases of *adenomata* of the cortical substance.

These show great diversity in their point of departure. They may proceed from the cortex itself, or may originate in the separated germs of the cortical system in the kidney, or in the genitalia, etc. The process concerned in such adenomata may be that of a simple hyperplasia, that may either run its course without symptoms or give rise simply to the local manifestations of tumor, or may assume malignant character, and then show great inclination for the formation of metastases. Finally these tumors may, without the mentioned tumor symptoms, lead to profound alterations of the organism, that with a certain probability may be regarded as the expression of a hyperfunction of the cortex. Before I enter into the consideration of the clinical manifestations, I should like to refer to the demonstration of *Bourneville* that in idiots with "sclerose tubéreause du cerveau" there are regularly found in the cortex of the suprarenals lumps that *Pellizzi* regards as adenomata of the suprarenals.

The hypernephromata consist in round, oval, or polygonal cells of an epithelial character. The cells are often of many shapes. As the suprarenals are of mesodermal origin, it is readily intelligible that the cells often assume a mesodermal character, and in their histological structure approach primitive sarcomata (*Glynn*). They are different, however, from the suprarenal sarcomata proper; true lumina are never observed in them (*Woolley*).

The simplest form clinically is represented by so-called *Grawitz* tumors. These may originate in the kidneys (*Grawitz*) or the ovaries (*Vonwiller*) or in the tail of the pancreas (*R. Mohr*). Lately their origin from separated germs of the suprarenals has been combated by *Stoerck* and *Zehbe*, while *R. Mohr* has again arrayed himself for this genesis. In the clinical respect it is significant that they are never associated with alterations in the genital sphere. This without doubt speaks for the view of *Stoerck* and *Zehbe*. At most we must assume that the *Grawitz's* tumors are strumas of the suprarenals that analogously to strumas of the thyroid do not tend to be associated with manifestations of hyperfunction.

When the *Grawitz's* tumors are of large growth they may lead to local oppressions (pains in the lumbar region, intercostal or femoral neuralgias, and when there is pressure on the kidneys to hematuria, albuminuria, cysturia, etc.), or they degenerate malignantly and lead to metastases and cachexia. *Westphal* has gathered twenty-four cases from the literature, and has added seven cases from his own statistics.

In *Grawitz's* tumor there is frequently a tendency to formation of cysts due to softening, with characteristic chocolate-colored content, which is eventually demonstrable on puncture.

It is true that *Westphal* adduces symptoms that indicate a hyperfunction of the chromaffin tissue. In two of seven cases he found temporary glycosuria, in three cases a relative increase in the neutrophilic cells and a distinct increase in blood-pressure in the early stages. I believe that these symptoms are only of a secondary nature, called forth by an initial irritation of the medullary substances by the growing tumor. It is worth mentioning that *Bittorf* in two cases of unilateral hypernephroma also found symptoms of an Addison's disease, emaciation, lassitude, pigmentations, and low blood-pressure. These cases also showed a lymphocytosis. It seems to me that this furnishes a corroboration of my view that the manifestations on the part of the chromaffin tissue (irritation or deficiency) are only of a secondary nature. *Bittorf* also observed slight psychical symptoms in his case and believes that they are of diagnostic importance and they do not occuri in tumors of the kidneys (*v. Strümpell*). Both *Bittorf's* cases were cured on operation, only the pigmentations remaining unaltered.

Perhaps the following two cases also belong to this group. *v. Neusser* mentioned a twenty-five-year-old man with very tense pulse, multiple hemorrhages in the brain. The section showed a carcinoma of one suprarenal. Vascular system and kidneys were normal.

In addition *v. Neusser* cites a case of *Fränkel's*, an eighteen-year-old girl with headaches, vomiting, and high tension of pulse. Section showed a vascular neoplasm of the left suprarenal; the kidneys were normal. Also here can the hyperfunction of the chromaffin tissue be regarded as an irritative symptom. Conversely in rapidly growing cortical tumors symptoms of deficiency of the chromaffin tissue may occur.

Of very great interest for the knowledge of the internal secretions are those adenomata of the suprarenal cortex that are associated with hyperfunction of the cortex. In the clinical picture of these cases there seems to be an appreciable difference according to whether they develop in the entirely childish, or in the juvenile or the adult organism.

I. With the development of such hyperfunctionating cortical tumors in the **childish organism** there occurs an enormously accelerated development of the body, a premature development of the genitalia. Such cases are described by *Cooke*, a seven-year-old female, *Tilesius*, a four-year-old female, *Ogle*, a three-year-old female, *Calcott-Fox*, a five-year-old female, *Orth*, two and one-half-year-old female, *Dobbertin*, four-month-old female, *Ritsche*, four-year-old female, *Bullock* and *Sequeira*, eleven-year-old female, *Linser*, five-and-one-half-year-old male, *Adams*, fourteen-and-three-fourth-year-old male. In the case of *Adams*, puberty set in at the age of ten years. The boy was large and strong muscularly. Autopsy showed tumor of the left suprarenal proceeding from the cortex. A careful compilation of the literature has been made by *Neurath*, and more recently by *Glynn*. Further cases are reported by *Guthrie* and *W. d'Este Emery* (four-and-one-half-year-old boy, fat, large tumor of the suprarenal cortex), by *Richards* (seven-year-old girl), by *Glynn* and by *French* (reported by *Glynn*); and perhaps also the case of *Guinon Bijou* belongs here (no autopsy).

Some cases I shall quote more exactly. The case of *Linser* was that of a five-and-one-half-year-old boy, who looked like a youth and therefore was admitted into the men's department of the hospital. He was 138 cm. tall, the penis was 8-9 cm. long, the testicles as large as pigeon's eggs, the prostate like that of a fifteen-year-old boy, the musculature was well-developed. The size of the body, the ossification, the almost complete set of permanent teeth, corresponded fully to those of a fifteen-year-old boy. The upper length was larger than lower length, hence childish dimensions were present *in a potentized form*. The hypophysis was normal and there was adiposity.

The case of *Bullock* and *Sequeira* was of an eleven-year-old female who looked like a forty-year-old woman. Menstruation had set in at the age of nine and three-fourth years and from this time on there developed an increasing adiposity. The girl was 4 ft. 6 in. high and weighed 6 stones, 3 lb. The breasts were fully developed. Long hairs were present on the genitalia. Autopsy showed a large tumor of the left suprarenal consisting in cells of zona fasciculata, with numerous metastases, hyperplasia of the thyroid and the parathyroids, fully developed uterus and large ovaries with corpora lutea of recent date.

The case of *Richards* was that of a seven-year-old girl. At the age of five she developed pubic hair and hair on the face. At seven years old she looked like a woman twenty years old, the hairs on the genitalia were fully developed, and hairs were present on the side of the face and on the site of the mustache.

The case of *Glynn* was that of a girl five years old. In the third year of life she began with pains in the abdomen and the head, later apathy. She was as large as a girl fourteen years old, and fat. Hairs were present on the upper lip, on the pubis and on the back. The sexual organs were especially well developed. There was found a large tumor of the suprarenal cortex, ovaries and hypophysis were normal. In the case of *French* (seven-year-old girl) the abnormal hairiness began to develop as early as the eighteenth month; the genital organs were very large; here also was found a suprarenal tumor.

It will be seen that the condition nearly always affects girls. Of seventeen cases collected by *Glynn,* fourteen were of the female sex. What is common to all in the clinical picture of these cases is, as *Neurath* emphasizes, the premature excessive development of the secondary sexual characters and of the external genitalia. *Neurath* mentions that in this category of premature sexual development, the function of the generative portion is on the contrary not prematurely developed. This does not always point to an especially intimate relation between the suprarenal cortex and the interstitial glands. Moreover common to almost all cases is adiposity, furthermore the accelerated growth, probably with retention of the infantile dimensions, and the accelerated ossification and dentition. The development of the psyche in such children as a rule does not keep pace with the bodily development. Also the development of the sexual instinct is mostly slow.

II. The manifestations that occur on the development of hypernephromata in *the juvenile or mature organism* are likewise characterized by an enormous influencing of the sexual sphere. Here also I would enter more fully in the case reports. The case of *Bortz* and *Thumim* was that of a sixteen-and-three-fourth-year-old girl. At first she had developed quite normally, then the menses ceased, and there developed a luxuriant deep black beard and a sparse mustache. Hairs developed on the chest and on the linea alba, the voice became deeper and universal obesity developed. Death occurred as the result of an intercurrent illness. Section revealed atrophy of the ovaries, enormous enlargement of the thyroid gland, normal hypophysis; on both sides there existed a suprarenal tumor rich in blood-vessels that had apparently developed only from the cortex.

Case of *Winkler.*—Sixteen-year-old girl. Abundant black hair on the upper lip. Uterus small. Tumor of the right suprarenal with metastases.

Case of *Bovin.*—Twenty-eight-year old woman. Two labors, then cessation of menses at the age of twenty-one. Development of the beard. There is also an abundant growth of hair on the abdomen. Simultaneously, the development of an abdominal tumor. Operation showed a large ovarian tumor proceeding from separated suprarenal germs. The patient recovered from the operation, the uterus became larger again, menstruation reappeared, and the abnormal hairiness disappeared. However, the observation after operation was for a short period of time only.

The case of *Hegar* perhaps belongs to this group (abnormal hairiness, uterus duplex, cystic tumor of the ovary). Moreover, perhaps also the case of *Alberti.* In this case menstruation was normal up to the nineteenth year. Development otherwise normal. Then set in hypertrichosis, development of a beard, mustache, and hair on the trunk. At the same time a tumor developed in the abdomen. Death occurred. Autopsy showed a cystoma pseudomucinosum proceeding from the right ovary. The clitoris was appreciably enlarged (autopsy only partial, no statement as to the suprarenals).

Case of *Goldschwend*.—Thirty-nine-year-old woman, had five children. Cessation of menses three years ago. For four months pains in abdomen, development of an abdominal tumor, development of a mustache and beard, and hair on the abdomen, malignant adenoma of the left suprarenal, uterus and ovaries small, epiphysis and hypophysis normal.

Case of *Launois*, *Pinard*, and *Gallais*.—Nineteen-year-old girl. Menstruated first at the age of thirteen years. At seventeen violent vomiting, gradually colossal obesity, mental changes. Cessation of menstruation, emaciation, then diffuse depilation, and only then hypertrichosis and myasthenia. The girl appeared to be much older than she was, black beard and mustache. Tumor of the right suprarenal.

Possibly also the following case of *Dalché* belongs here; twenty-eight-year-old woman, body quite feminine, for five years development of a mustache and beard and (after miscarriage) cessation of menstruation. Breasts well developed, voice feminine, uterus small, atrophy of the inner genitalia, hypertrichosis on abdomen, slight manifestations of hyperthyrosis, there were no other symptoms of a suprarenal tumor.

Also a case has been reported that began at the menopause.

Case of *Santi*.—Fifty-three-year old woman, two normal pregnancies, menstruation always regular until six years ago. Then the periods became more frequent, until the woman lost blood almost constantly. Enlargement of the abdomen, enormous obesity. Autopsy showed a tumor of the kidney proceeding from separated suprarenal germs, and a similar tumor of the ovary. No statement as to hairiness.

Under this category may well belong the case of *Vollbracht*, mentioned by *v. Neusser* and *Wiesel*. The case was designated by the last named authors as Addison's disease with contrasexual sexual characters.

Let us look over the cases I have mentioned. In women simultaneously with the development of a hypernephroma there occur cessation of the menses, hypertrichosis of a definite localization (linea alba, growth of beard) and obesity. The development of hypernephroma at the menopause apparently gives rise only to obesity.

III. Cases of *Pseudohermaphroditism*.—*Marchand* first reported the autopsy findings in a fifty-year-old individual who in life was always regarded as a man.

The individual showed masculine body conformation and masculine hairiness of the face; autopsy showed a hermaphroditismus spurius femininus, a very large penis-like clitoris, a distinct scrotum and a rather large prostate; there was also a vagina with the traces of a hymen, a uterus, and atrophic ovaries. Finally *collosal hypertrophy of the suprarenal cortex and a large accessory suprarenal.* A similar case had previously been reported by *Creccher.*

Three cases of pseudohermaphroditismus femininus by *Fiebiger:* Habitus and hairiness quite masculine, larynx masculine, penis and prostate present, no vasa deferentia, vagina, uterus, and ovaries. The last showed the follicle formation. No menstruation; capable of cohabitation. Masculine sexual sense. Very large suprarenals, apparently hyperplasia of the cortex. *Fiebiger* regards these cases as an especially teratological type.

Case of *Engelhardt.*—Fifty-nine years. Married a woman at the age of twenty-seven years. Erections were present, but only weak and very rare. Questionable whether ejaculations were present. Beard and mustache. Facial features masculine. Breasts feminine, hands and feet slender. Penis embedded in a cushion of fat. Hypospadia, corpora cavernosa present. Scrotum only indicated by tissue rich in fat, testicles, buttocks, hips and thighs are feminine. Prostate feebly developed. Autopsy showed an aberrant suprarenal struma at the lower pole of the right kidney. The ovaries were small and dense, with sparse, poorly developed, follicles.

Here also belongs the case of *Hepner* and *Ogston* and furthermore the very interesting case of *Meixner* (case III). This was the case of a new-born child with pseudohermaphroditismus masculinus, bilateral cryptorchidism, with separated and enlarged suprarenal glandular tissue in the neighborhood of the testicles.

*v. Neugebauer* mentions in his large work thirteen cases of pseudohermaphroditism with suprarenal tumors.

Summarizing the cases cited: only one case was that of pseudohermaphroditismus masculinus. The other cases were pseudohermaphroditismus femininus. All cases showed a bilateral swelling of the suprarenal cortex.

IV. Finally it should be remembered that also in acromegaly there occur certain cases in which hyperplasia of the suprarenals is observed (*Delille*, *Fischer*, and *Fischer* and *Schultze*). *Fischer* and *Schultze* find the entire suprarenals, cortex as well as medulla hyperplastic, while *Delille* observed only a hyperplasia of the cortex. It is very probable that in the future when we pay more exact attention to these relations that we will find hyperplasia of the suprarenals, and especially of the cortex, in many cases of acromegaly. I would also call attention to the fact that in many cases of acromegaly, there occurs both in men and women abnormally abundant hairiness. In women the hairiness may assume quite the masculine type.

Surveying the entire field of facts, one is surprised by the wealth of clinical observations that properly classified demonstrate that from the suprarenal cortex there goes forth an enormous influence on the growth of the body, on the genital sphere, and on the hairiness, therefore on an important secondary sexual character. Until a short time ago these connections were scarcely suspected. In the books of *Neusser* and *Wiesel* on the diseases of the suprarenal glands they are hardly taken up. As to what concerns the alterations in the organisms that occur in hyperplasia of the suprarenals, that is in conditions of hyperfunction, it is worthy of note that they are different according to the age at which such hyperplasia develops. Their action occurs earliest in pseudohermaphroditism. Here their development occurs in fetal life. That the development of such cortical hyperplasias stands in a causal relationship with the development of pseudohermaphroditism is hardly at all probable; as up to the present insufficient attention has been paid to such relationship, it would not do to assume that the hyperplasias occur constantly in pseudohermaphroditism. It is much more likely that they are only a partial manifestation of the malformation, which would lend to them at all events a definite expression. It has already been mentioned, they occur almost exclusively in pseudohermaphroditismus femininus.

In the age of childhood we see with development of the tumors of the suprarenal cortex a premature development of the entire organism, a sort of transient gigantism associated with potentized childish dimensions and premature development of the genital organs, a clinical picture that in almost all respects is similar to that observed in the development of tumors of the pineal gland in childhood. Whether hyperplasia of the suprarenal cortex is frequently present with tumors of the pineal in childhood is as yet not certain. Up to the present it has been observed in one case only. As we shall see later in the development of tumors of the sexual glands in childhood there occur the same clinical pictures, even, if possible, better pronounced. Here also future studies must decide as to the behavior of the suprarenal cortex. Apparently there exists an intimate connection between these three forms of premature development and it would not be unlikely that the bond of union is the suprarenal cortex. At any rate, a certain influence of the suprarenal cortex on the growth is evident; with this agrees also the occurrence of cortical hyperplasia in acromegaly. Just as evident is a certain stimulating influence on the development of the sexual glands. Apparently there exists here a reciprocal correlation, as hyperplastic changes in the suprarenal cortex occur during rut in animals and in pregnancy (*Guiyesse*, *Stoerck* and *v. Haberer*). In this also can be seen a certain relation of the suprarenal cortex to growth. As is known, women who are pregnant and whose epiphysial junctures are still open often take on a renewed growth during the pregnancy. And finally there can be seen on it a relation to the growth of the fetus, if it be not forgotten that the hyperplastic alterations in the anterior lobe of the hypophysis may also produce and maintain the tendency to increased growth.

When the cortical tumors develop in the fully developed organs the manifestations are quite different. Thus far the cases have been favorable. Here there comes about a pronounced disturbance of the functions of the sexual glands with involution of the uterus and in addition a tendency to obesity and to the development of hairiness, both of which with respect to abundance and localization are entirely masculine. The influence of the suprarenal cortex on the hairiness is especially unmistakable in all the conditions mentioned. We find abnormal hairiness in pseudohermaphroditismus femininus, in the premature development in childhood, in the cortical tumors that develop in the adult organism, perhaps just in the cases of acromegaly with hyperplasia of the cortex, and finally, as is known, in pregnancy, where hair begins to grow in places that otherwise represent the virile type. Therefore it seems necessary that in future, when the question is asked as to which influences the secondary sexual characters have to thank for their origin, attention should also be paid to the suprarenal cortex. The near relationship that the suprarenal cortex and the substances of the sexual glands show embryologically and morphologically seems also to exist in the function of these parts.

**Treatment.**—Up to the present, only the operative treatment of hypernephromata has been tried. In every case an early diagnosis is important, as the tumors are often malignant. That result may be expected from operation is shown by the previously mentioned case of *Bovin.* Perhaps in certain cases a result may be expected from the use of the X-rays.

### 3. Tumors of the Suprarenals that Apparently Consist in Cortex and Medulla

*Davidsohn* has reported a case of melanoma of the suprarenals with numerous melanotic metastases. Histologically were found cells of the zona fasciculata and glomerulosa, but also cells of the medulla. The metastases, on chemical examination and on blood-pressure tests, were found to contain adrenalin. Moreover, perhaps here belongs the case of *Neuberg,* in which indeed no adrenalin could be demonstrated, but in which an enzyme was found which could change adrenalin into a black pigment. *Neuberg* believed that the adrenalin further produced in the metastases was the mother substance of the melanin found there. These cases were not accompanied with disturbances of the sexual sphere.

### Addendum

*Glynn,* from a review of the literature, arrives at about the same opinions as the author with reference to the relation of the suprarenal cortex to the other ductless glands and to sex. He adduces as a further argument for the view that renal hypernephromata arise from suprarenal rests the fact that such rests are rare in the kidney, while hypernephromata are common kidney tumors; and that suprarenal rests in other localities, though comparatively common, especially in early life, rarely produce tumors at all.

*Cannon*, *Shohl*, and *Wright* subjected cats to fright, and uniformly obtained glycosuria. This glycosuria was not present after adrenalectomy.

*Glynn* (*E. E.*). The adrenal cortex, its rests and tumors; its relation to other ductless glands and especially to sex. The Quarterly Journal of Medicine, Vol. V, 1911–1912, p. 157.

*Cannon* (*W.*), *Shohl* (*A. T.*), and *Wright* (*W. S.*). Emotional glycosuria. Am. J. Physiol., 1911–1912, pp. 280–287.

## CHAPTER IX

# STATUS LYMPHATICUS AND STATUS HYPOPLASTICUS

### A. Status Lymphaticus

Here at the conclusion of the discussion of the suprarenal apparatus we might add some remarks on the so-called status lymphaticus, because recent investigations have shown that it possesses a close relation to conditions of hypofunction of the chromaffin tissue. As I have already mentioned in the chapter on the thymus gland, the tendency among many authors is for the separation of status thymicus from status lymphaticus. The frequent coincidence of a large thymus gland and status lymphaticus can perhaps be explained by the increase in the lymphoid elements in the thymus gland. The great interest that clinicians and pathological anatomists have turned on status lymphaticus depends on the fact that it is associated with cases of sudden, quite inexplicable, death. It is the great service of *A. Paltauf* to have recognized that here there is an underlying profound constitutional alteration, which is always associated with lymphatism.

How, now, is status lymphaticus characterized? Here it seems that I must give vent to a conception that has forced itself upon me especially in the study of the diseases of the ductless glands. I am forced to distinguish a *primary* and a *secondary* lymphatism. The first develops in earliest youth, and has on this account a profound influence on the development of the whole organism. It is characterized by the following earmarks (in this I follow the description of *A. Paltauf* and especially the new excellent description by *Kolisko*). Under normal circumstances we find that in childhood the lymphatic apparatus is essentially more strongly developed than in adults. Hence it comes about that the leucocytic formula of the child shows a greater content of lymphocytes. The years of childhood are those in which lymphatism is especially prone to develop. The involution of the lymphatic apparatus follows, chiefly at puberty. In true status lymphaticus the involution of an already abnormally developed lymphatic apparatus remains absent. We find enlarged follicles at the base of the tongue, hyperplasia of the entire pharyngeal lymphatic ring, lymphoid growth in the nose, enlargement of the lymphatic glands in the neck, in the axillary and inguinal regions, hyperplasia of *Peyer's* patches, red bone marrow, large spleen, and more or less large thymus gland. Very frequently we found hypoplasia and narrowness of the aorta and the whole arterial vascular tract. The heart likewise is often abnormally small, although it can also be hypertrophic. Commonly there is dilatation of the left ventricle with diffuse clouding of the endocardium, and not rarely remaining behind in the development of the genitals, slight development of the secondary sexual characters, retarded onset of menstruation, and retarded, lessened, sexual instinct.

According to the new researches of *Wiesel* and *Hedinger* there is regularly associated with these characteristics an abnormally slight development of the chromaffin tissue. The medullary substances of the suprarenals is essentially lessened, and also the paraganglia are illy developed. According to *v. Sury* this underdevelopment of the chromaffin tissue mostly sets in after birth.

In status lymphaticus there occurs in the blood picture a relative or absolute reduction of the neutrophilic leucocytes and a corresponding increase in the mononuclear cells, eventually also a hypereosinophilia (*v. Neusser*). This fact is readily intelligible when the experiments of *Bertelli, Schweeger*, and *myself* are considered. On the one hand it is possible that the giving off of mononuclear cells of the blood is increased in hyperplasia of the lymphatic apparatus, and on the other hand we must assume that an enormous trophic influence is exerted on the production of the neutrophilic elements of the bone marrow, this influence proceeding from the chromaffin tissue by mediation of the sympathetic; here the production of neutrophilic elements by the bone marrow is probably diminished.

It is very possible that this anomaly of constitution is the cause of the sudden death. If the chromaffin tissue is underdeveloped and not attained to a great functional breadth, it may, if especial demands are made on it especially by a cold bath or by the effects of narcosis of the sympathetic nervous system, suddenly give out. This form of status lymphaticus may well be designated an "entité morbide." Also the opinion has been expressed that substances are given off from the lymph-glandular system to the blood path, substances that in their action are in a certain way antagonists of adrenalin (*v. Neusser*). Also in this sense can we consider this form of status lymphaticus under the diseases of internal secretion. Such individuals as *Eppinger* and *Hess* mention not rarely show symptoms of the relatively increased vagal tonus (inclination to sweats, certain anomalies of the pulse and respiration, etc.). The slight functional breadth of the chromaffin tissue is, however, especially important for the fate of such individuals. Often the blood-pressure lies near the lower limits of normal, as *Münzer* emphasizes, the pulse shows a slight force [Wurfkraft]. According to *Wiesel* such individuals are especially predisposed to Addison's disease, in that tuberculous and other processes become established in the hypoplastic suprarenal medulla, and by spreading to the cortex call forth the typical picture of Addison's disease.

The *secondary* form of status lymphaticus is characterized by the fact that the signs of lymphatism predominate only later, the development originally being normal. According to the age of the individual, according to whether the lymphatism is only transitory or remains permanent, does the development become more or less inhibited. In childhood, as already *H. Kundrat* mentioned, rachitis leads to lymphatism not infrequently, as do also tetany, the exudative diathesis, especially scrofulosis, and a series of other infectious processes. In adolescent and adult individuals occasion is given for a temporary or a permanent lymphatism by vagal neuroses, bronchial asthma, chronic infectious diseases, especially lues and tuberculosis, osteomalacia, and especially the affections of the ductless glands. In a great number of cases perhaps there occurs at first, through chemotactic influences, only a slight mononucleosis of the blood, and only later a slight hyperplasia of the lymphatic apparatus, therefore a forme fruste; in other cases, especially in many formations of ductless glandular affections, the hyperplasia of the lymphatic apparatus may be fully developed. Of the ductless glandular diseases should be mentioned especially Addison's disease, myxedema, Basedow's disease, acromegaly, tetany, and dystrophia adiposo-genitalis. Also in some cases that we must regard as true eunuchoids we found appreciable mononucleosis of the blood. It is self-evident that mononucleosis is a symptom with many meanings, and in itself speaks nothing for the diagnosis of status lymphaticus. Thus we found it strikingly present also in many severe forms of diabetes mellitus in which autopsy showed no status lymphaticus. It is very probable that under secondary lymphatism are concealed numerous and diverse conditions, in part chronic inflammatory in nature, the differentiation of which perhaps can first be made by a careful microscopical examination of the lymphatic apparatus.

The great difficulty in the *diagnosis* of status lymphaticus in vivo is made prominent in the comprehensive exposition of this subject brought out a short time ago by *v. Neusser*. *v. Neusser* relates how important it is to have in mind, in consideration of the minute factors, the possibilities of an existing status lymphaticus, because the infectious diseases and especially the most diverse noxious agents frequently take on a characteristic expression on the ground of this constitutional anomaly and often pursue their course unfavorably.

### B. Status Hypoplasticus

In several works, *Bartel* has indicated a form of developmental disturbances that he designates *hypoplastic constitution*. It is frequently, but not always, associated with status lymphaticus. The body size of such individuals is on the average normal. Often the fatty tissue is very well developed. There is found hypoplasia and narrowness of the vascular system and poverty of the smooth musculature of the aorta (*Wiesner*), and in addition faulty development of the sexual glands and secondary sexual characters. The sexual glands are indeed of normal size, the ovaries often even enlarged; microscopically there is found, however, proliferation of the connective tissue (*Herrmann* and *Kyrle*). When status lymphaticus is present an atrophic stage can follow the stage of hyperplasia. *Bartel* assumes as the cause of this condition congenital predisposition on the one hand, and on the other hand damaging of the sensitive childish organism, especially by infectious diseases. The length of life of such individuals is mostly shortened, and 56 per cent. of the cases investigated by *Bartel* died between the fourteenth and twenty-fifth years of life. The status hypoplasticus is thus not entirely identical with status lymphaticus, but also not with true infantilism, which will be described in another chapter.

## CHAPTER X

## THE DISEASES OF THE SEXUAL GLANDS

The knowledge of the internal secretion took its origin from the sexual glands. *Brown-Séquard* injected himself with testicular extract and believed that thereby he could obtain a sort of rejuvenation of the organism. The experiments on the sexual glands also first brought the knowledge that the function of the ductless glands is in a high degree independent of the nervous system. *Goltz* transected the spinal cords of animals and observed that these animals conceived, carried their young normally, gave birth and suckled, in spite of the fact that the ovaries were cut off from the higher nervous centers. The later researches on transplantation of the sexual glands showed this independence in still higher degree. *Ribbert* and later *Knauer* transplanted the ovaries under the skin in animals and observed that in such animals there occurred no involution of the uterus such as would otherwise tend to occur after castration. *Halban* showed that also in the youthful incomplete organism transplanted ovaries could exercise their protective influence on the development of the genital apparatus. The ovaries were transplanted under the skin of new-born guinea-pigs. After one year *Graffian* follicles and ova were present in the transplants. Uterus and breasts developed normally, while in the castrated control animals breasts and genitalia remained quite rudimentary. *Foges* and later *Steinach* then showed that after transplantation of the testicles the secondary sexual characters develop (although not always completely), while in the castrated control animals the development of these characters suffer marked damage.

While not until lately has experimental pathology furnished an insight into the function of the sexual glands, clinical observation from the very beginning has stirred the interest of physicians and the laity, because the instinct of procreation affects everything that lives. The influence that the loss of the sexual glands exercises on the configuration of the body and the development of the secondary sexual characters has been known since antiquity. Just those malformations that stand in especial relations with the sexual glands such as hermaphroditism, or the development of the so-called contrasexual character, belong to these curiosities that since that time have been exhibited in show-booths [museums]. Also the problem of heredity is intimately associated with the function of the sexual glands.

Finally there comes the great practical significance that this problem has always had for breeders of animals.

**Embryological, Anatomical, and Physiological Preliminary Remarks.**—For the comprehension of the physiology and pathology of the sexual glands it is necessary to distinguish sharply between these proper and the accessory genital apparatus. The rudiments of the accessory apparatus (primordial kidneys with *Wolffian* and *Müllerian* ducts) are common to both sexes. According as to whether sexual glands develop into testicles or ovaries do the indifferent rudiments develop into epididymis, paradidymis, vasa deferentia, and prostate or into epoophoron, paroophoron, *Gärtner's* ducts, tubes, uterus, and vagina.

Two parts of the sexual glands are to be distinguished: the interstitial glands[1] (consisting in the so-called *Leidig's* interstitial tissue), and the specific glands of generation (in man, seminiferous tubules, *Sertoli's* cells(?) in women, the follicular apparatus).

## A. The Interstitial Glands

The *Leidig's* interstitial cells are epithelioid cell accumulations imbedded in the sexual glands of the male. They are filled with acidophilic and basophilic granules, show great similarity to the cells of the suprarenal cortex, and like these are of mesodermal origin (*Simon*, 1892, *Wallart*, *Seitz*). Especially enormous is the development of these cell formations at the time of puberty. In women we understand by "interstitial glands" a cell complex that develops from the atretic follicles of the theca interna. Also in women is the development of these cells very distinct at the time of puberty, also temporarily during pregnancy (*Wallart*). I must not omit to state that the view is held by many that in the highest female mammals, in the human species and in monkeys, the interstitial glands are inconstant (*Bucura*). This had been denied on other sides, and I would only state here that the function of the interstitial glands in man is to-day already so sharply delimited and that it is concerned with functions so important, functions that influence the conformation of the body in such an extensive manner, that it is hard to believe that so important an organ is absent in women.

According to the view of some of the authors the interstitial glands govern in man in this special field the development of the primary and secondary sexual characters, and are hence of great importance for the formation of the body.

The distinction between interstitial glands and generative apparatus is based on a series of clinical observations and experimental facts. The clinical observations, which I shall describe first, are concerned with cryptorchidism.

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[1] The distinction between "internal secretory and germinative" that up to the present has been the practice in the literature, and that was also retained by me in my article on the diseases of ductless glands in *Mehr-Stachclin's* handbook, must be rejected by me, as it seems to me to lead to the coarsest misunderstandings. *Steinach* designates the "innersekretorische" glands as "Pubertatsdrüse." It seems to be undoubted however that the "internal secretory" activity of the generative apparatus is very considerable. Indeed the entire teaching of hormones has been developed from the influencing of the growth of mammary glands through the hormone of the fetus or of the chorionic epithelium, that is to say properly, the ovum.

*Variot* first pointed out the great difference between kryptorchides abdominaux and kryptorchides inguinalis. The first is associated with obesity and broadening of the pelvis; the larynx remains small, the voice remains high and shrill, the beard and the pubic hairs do not grow; microscopical examination shows marked connective tissue proliferation in the extremely small testicles. I shall speak of this form later in the consideration of eunuchoidism.

In the adult kryptorchides inguinales, in which the testicles remain behind in the inguinal canal, the sexual potency may be present. Such individuals may have ejaculations without the expulsion of spermatozoa. They are therefore potent, but sterile. These individuals have an entirely masculine habitus, the voice changes, there occur growth of beard and normal hairiness of the trunk, the musculature is vigorous, the dimensions of the skeletons are normal, etc. Here the function of the interstitial glands is retained, while that of the generative glands are not developed. In twenty cases of cryptorchic testicles, *Tandler* found no spermatogenesis in a single case, but did find normal interstitial substance. Therefore, in cryptorchidism the disturbance in the development of the glands of generation is the rule, while the disturbance of that of the interstitial glands is found only in severe cases.

The first experimental observations were made by *Ancel* and *Bouin*. They ligated the vasa deferentia and found that after a time spermatogenesis had entirely disappeared, while interstitial glands were retained. These animals showed complete normal development of the masculine habitus. *Tandler* and *Grosz* further showed that after intensive Röntgen irradiation of the testicles of young Cerviden the spermatogones, on account of their greater sensitiveness become destroyed, while the interstitial glands were retained. In these animals the masculine sexual characters developed in entirely normal manner. Latterly *Simmonds* has shown that after Röntgen irradiation there are always found individual undamaged seminal tubules, that can again regenerate; but the significance of this finding must not be estimated too high. Lately *Steinach* has reported concerning transplantation experiments that place the matter in a secure position. If in young sucklings the testicles are transplanted, the secondary sexual characters proceed to develop entirely normally. The histological examination shows that the spermatozoa are entirely absent. Clinical observation was thus entirely corroborated by experiment.

As in such animals also the external genitalia develop entirely normally, it is to be assumed that the interstitial glands exercise an important influence:

1. On the development of the generative glands. An isolated development of these without the interstitial glands is not known in the male sex.

2. On the accessory genital apparatus.
3. On the so-called secondary sexual characters.

Hence the question is explained in the male sex. As has been mentioned it is hard to assume that in women such an important organ should be absent.

Although it is now established that the interstitial glands exercise an entirely essential influence on the development of the secondary sexual characters, we must still regard the question of the genesis of the secondary sexual characters and their relations to the sexual glands as one that is much argued. There is no uniformity in the definition, even of the secondary sexual characters. *Darwin* understands by them any sexual characters that are characteristic for the sex in question, but which have nothing directly to do with reproduction.

*R. Müller* divides the secondary sexual characters in to physical and mental, and further divides them into:

1. Such as have entered into an intimate relationship with the propagation and nurture of the young animals: for example, female pelvis, mammary glands, temperament, sexual instinct, maternal love.
2. Such in which are shown an immediate dependence on sexual glands: skeleton, muscular system, skin-appendages (antlers, horns, combs, etc.), formation of the larynx, swelling of the thyroid gland, etc.
3. Such that are only mediately dependent on the sexual glands: internal organs, different psychical activity, etc.

I wish from the beginning to limit myself to these two definitions. My attitude toward them will be stated later.

First I shall describe more in detail the distinguishing features between the [human] male and female bodies, following the exposition of *Novak*. The female and male bodies are far more like each other up to the time of puberty than later. Before puberty both show the infantile type, although extensive differences exist even in the earliest period of embryonal life. For instance the pelvis may be recognized as feminine as early as the fifth month of embryonal existence (*Fehling*). At the time of puberty the growth in both sexes is essentially increased. In the male the larynx now enlarges, the voice changes, the growth of the beard begins to be more evident; in the female, the breasts develop, the characteristic form of pelvis becomes more prominent, the figure becomes rounded and an abundant deposit of fat is found especially on the hips. In both sexes there now occurs a growth of pubic and axillary hairs, the former in women remaining bounded above by a horizontal line, while in man it closes above in the form of a triangle. In man the body size is on the average greater, the horizontal circumference of the head is slighter in relation to the body height, in woman the capacity of the head is less, as is also extension of the facial part. In man the extremities are longer in relation to the length of torso, in woman this is reversed. In women the shoulder-girdle is relatively small, the hips are broader. The hairs of the head in woman are much longer, the hairiness of the body is absent. *Michaeli's* quadrangle is broader in woman, the sacrum is less curved and is shorter, the symphysis is broader and lower, the pubic angle is greater, the iliac fossæ are broader, the transverse extension of the pelvis is greater, the pelvic entrance and exit are greater and wider. The glandular substance in the breast is always developed even in the virgin, the nipples are more prominent, and more easily erectile. In addition there is in woman a less number of erythrocytes per cubic millimeter of blood. Then there are differences in the psyche, that become more prominent from the time of puberty.

I would now briefly sketch those problems that seem to me most important for the evaluation of the secondary sexual characters and for their genesis.

Almost all of the distinguishing signs that have been mentioned may be included under *Darwin's* definition. The mammary glands seem to me to form an exception. Much seems to speak for the fact that the female mammary glands are a primary sexual character, or rather that they should be directly ascribed to the generative apparatus. We cannot say of them that they have nothing to do directly with propagation, for in mammals the brood would be annihilated if the mammary glands were to cease to functionate. We can, however, go farther and suppose that the growth impulse that the mammary glands experience in women emanates not from the interstitial glands, but from the generative apparatus, that there exists no development of the glandular substances (certainly not of the fat substances) without development of the follicular apparatus, and that the most extensive growth impulse, namely that during pregnancy, proceeds from the generative apparatus, equally if we regard as the source of the mammary hormone the growing fetus or the chorionic epithelium. We shall enter more fully into this question later.

A further moot point is whether the secondary sexual characters are preformed from the ovum—as to the question whether before or after conception, I shall not enter into here at all—or whether they develop in the masculine or feminine direction under the influence of the sexual glands. *Lenhossek* and *Halban* hold the opinion that the total sexual characters are somewhat preexistent and that the sexual glands exercise only a protective action on their development.[1] Another view that stands rather bluntly opposed to that just described is that the sexual glands furnish a direct formative stimulus on the sexual characters. Recently *Steinach* on the ground of transplantation experiments inclines to this view. Finally *Biedl* supposes a hermaphroditic rudiment of the sexual glands. The secondary sexual characters develop either in a masculine or a feminine direction according as to whether the development of the masculine or feminine internal secretory sexual glands predominate. The occurrence of heterologous sexual characters is explained by *Biedl* by the supposition that the internal secretory portion of the sexual glands that belongs to the other sex obtains the upper hand.

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[1] Also *Tandler* upholds the opinion that the sexual sphere of action of the secondary sexual characters as well as those of the germinal glands are preexistent. *Tandler* and *Grosz* mention in this connection that the so-called secondary sexual characters are only characters of species and enter into relation to the genital sphere only secondarily.

A further problem lies in the fact whether the sexual characters in their development especially depend exclusively on the sexual glands, or whether much more do they not rather receive decisive influences from the other ductless glands.

The discussion of all these questions makes necessary not only the resort to experimental pathology and physiology, but to an abundance of clinical observations. It seems to me therefore suitable to describe first the generative apparatus, then to detail the most important clinical observations and only later to enter into the discussion of these questions. I need hardly emphasize that judging from the contradictory nature of the opinions, the discussion must be strongly tinged subjectively.

## B. The Generative Apparatus

As previously mentioned, the interstitial glands are of mesodermal origin. This has also been assumed for the generative apparatus, although to me the view seems very noteworthy that the generative apparatus (spermatogonia in man, follicular apparatus in women) develop out of the primordial cells. Then the interstitial glands and generative apparatus are differentiated embryologically. Primordial follicles and *Sertoli's* cells are demonstrable already at an early embryological stage.

We shall first take note of the development of the generative glands and their influence on the total organism, in *woman*. The development of the follicular apparatus is quite gradual. First at the time of puberty, together with the beginning of maturation of the interstitial glands does it come to full development; at the same time too with an enormous growth impulse for the breasts and the beginning of menstruation. While now in man after complete maturity there enters the condition of rather continuous function of the sexual glands and especially the generative apparatus, in woman is the activity of the sexual glands and especially of the generative apparatus subjected to periodic variation. With the periodically recurring ovulation and menstruation, enters in the vital processes a noticeable wave movement that has been deeply studied by *Goodman*, *Jacobi*, *Rabutau*, *Reinl*, *Ott*, and *others*. There is the premenstrual period, the period of menstruation and the postmenstrual interval to be distinguished. During the premenstrual period there are found signs of a gradually increasing vitality of the internal organism, that rapidly reduces during the bleeding. In the seven or nine days immediately before menstruation the blood-pressure increases, it falls rapidly with the beginning of the flow, and reaches its lowest value at the close of the period. With this variation in blood-pressure are associated variations in the erythrocyte count. In the premenstrual period the erythrocyte count may lie 1 to 1½ millions higher than toward the end of menstruation. It is very possible indeed that just as in tetany, these variations in the erythrocyte count are to a great degree the expression of an increased or diminished tonus of the vessels; for which view speaks also the careful blood-pressure measurements. In connection with it may stand too the strong permeation of many organs with blood. Moreover in the premenstrual period there is found a higher level of bodily temperature that becomes prominent especially in latent diseases (*Reinl*). On the day preceding and the day following menstruation the temperature is the lowest. In many individuals there may also be demonstrable, in the premenstrual period, a slight neutrophilic hyperleucocytosis and a slight heightening of the coagulability of the blood. Also the respiratory volume is often raised in the premenstrual period, while it is slightly decreased during menstruation (*L. Zuntz*). Many of the manifestations detailed seem to me to point to an increased function of the chromaffin tissue. With this may be connected the observation that in the premenstrual period the glycosuric action of adrenalin is heightened. Moreover there is found an increase in reflex excitability and often a higher mental alertness and capacity, while during menstruation there often occurs a certain mental obtuseness. Known for a very long time is the swelling of the thyroid gland in the premenstrual period (struma antemenstrualis, *Heidenhain*). It is further stated that before rut and in the premenstrual period the suprarenal cortex increases in size. Also the interstitial glands show the same behavior during this period, apparently also does this hold true for the glandular hypophysis. At least such a conclusion seems suggested by the similar alterations of these ductless glands during pregnancy; perhaps is also found in the premenstrual period an increased growth of any beard that may be present (*Halban*). Finally it is known that the mammary glands often swell slightly, and in rare cases even in the virgin may come to a slight secretion of colostrum. Further the nipples often show an increased erectibility and are painful.

What now is the cause of this rhythmically occurring menstrual wave? *Pflüger* developed a theory that monthly ovulation leads by reflex paths to a hyperemia of the pelvic organs, thereby causing menstruation. *Pflüger's* law has been made untenable by the knowledge that the influence of the ovaries in the organism is independent of the nervous system and depends on the giving off of substances to the blood-path. Hence it must be modified to state that the influence of the internal secretion of the generative apparatus on the organism is, through the maturation of the ovum, increased in a rhythmic manner. It is now urged against the dependence of menstruation on ovulation that not rarely menstruation and ovulation do not occur at the same time, but that under circumstances ovulation can take place after menstruation (*Leopold* and *Mironow, Ravano*). *Fränkel* has therefore upheld the view that the retrogression of the corpus luteum gives rise to menstruation. According to the view of most authors there can, however, be attributed to corpus luteum at most a postponing but not a releasing [auslösende] action (*Halban*). *Halban* would principally ascribe to the ovulation, that is to the sexual glands, only a protective but not a formative influence on menstruation or on rut and on the cyclical menstrual phenomena, pointing out the known fact that after even a long time after bilateral ovarectomy the menstrual wave may reappear. Numerous extensive statistics exist as to this question; I mention only the statement of *Pfister* that in on an average of 12 per cent. of castrated women menstruation reappeared and that among 116 castrations vicarious menstruation from the bowel or the nose occurred for a time in cases. Finally it must be pointed out that in a great percentage of cases after castration there exist cyclical menstrual molimina (backache, nausea, colics, etc.). Of course these molimina occur when the uterus is removed and the ovaries remain behind in the body. *Halban* is therefore of the opinion that the menstrual wave is released not from the ovary itself, but by an as yet unknown agent and that much the more the ovary itself reacts to this agent in an especially sensitive way, and this reaction of the ovary first brings the menstrual wave to its complete fulfillment.

I would not subscribe unreservedly to the view of *Halban*. The dependence of menstruation on ovulation is in any case very considerable. *Halban* himself has shown that in baboons, which have a menstruation similar to that of human beings, menstruation is retained after transplantation of the ovaries. On the other hand after ovarectomy, rut remains away with almost every case. Lately *Adler* has shown that subcutaneous injection of watery extract of ovaries calls forth in virginal animals alterations in the internal genitalia, especially the uterus, that remind one of the changes that take place during rut. In two amenorrheic women in whom pieces of mucous membrane were obtained from the uterus by curettement before and after injection of this extract, microscopical examinations of these pieces showed that there were menstrual alterations of the mucous membrane. As after castration the menstrual wave is recovered after a time in an attenuated form, this does not seem to me quite inexplicable. We can imagine that the menstrual wave that has existed for several years may under circumstances continue for a while after castration, if the sexual life has once been fully developed. The difficult point according to my view would lie in the question whether, in youthful persons in whom menstruation is chiefly absent, the development of the wave would be entirely prevented by castration. I believe that this would be the case, just as the sexual life fails to develop in those castrated in early youth. The circumstance that ovulation and menstruation do not always occur at the same time does not seem to me very essential. It is conceivable that the acme of the internal secretory function of the maturing follicle and the reaction of the organism due to this in many cases occur before the extrusion of the egg, in fashion similar to that which *Halban* assumes for the function of the chorionic epithelium in pregnancy. While therefore ovulation is independent of menstruation, ovulation may continue to exist when menstruation is absent. This is satisfactorily demonstrated by the fact that women a long time amenorrheic may conceive. Indeed ovulation may take place in women who have never menstruated; then are found eventually only cyclical swelling of the uterine mucous membranes, or cyclical leucorrhea (*Ogórek*).

**Pregnancy.**—Even after fructification the ovulation shows certain starts [Ansätze] (*Ravano-Fellner*), then it ceases entirely, and menstruation ceases with it. The corpus luteum persists. Probably the cessation of ovulation is to be referred to persistence of the corpus luteum, or both manifestations are to be referred to the developing fetus or much more to the development of the chorionic epithelium. I cite the following from known facts that are important for the understanding of these relationships. In the cow there not rarely occurs persistence and hypertrophy of the corpus luteum. Then rut ceases. If the corpus luteum be removed, rut recurs. Moreover *Kleinhans* and *Schenk* showed the extirpation of the corpus luteum alone does not lead to interruption of pregnancy, therefore the development of the fertilized egg is not dependent on corpus luteum.

Pregnancy leads to profound changes in the maternal organism. According to *Neumann* and *Hermann* lipoidemia can always be demonstrated. They found the lipoidemia also after castration and in the climacteric period. I would refer it especially to the cessation of the activities of the follicular apparatus. Further, during pregnancy, are found signs of a heightened excitability of the vegetative nervous system. *L. Pollak* could show during pregnancy heightened glycosuric action of adrenalin. The statement as to an increased adrenolinemia in pregnant women (*Neu*) could not be corroborated by *Neubauer* and *Novak*.

Very commonly in the latter stages of pregnancy is found a neutrophilic hyperleucocytosis. Further the temperature is placed at a higher level, and also the blood-pressure and the pulse rate are higher.

Also investigations on the metabolism have shown that there are profound alterations. *Falk* and *Hesky*, and *Zangemeister* found relative increase in the ammoniacal nitrogen, *Leersum*, *Rebaudi*, and *Falk* and *Hesky* found increase in the amino acids, the authors last-named also an increase in the polypeptid nitrogen, and *Salamon* and *Saxl* an increase in the elimination of oxyproteinic acid. The tendency of pregnant women to alimentary glycosuria and alimentary levulosuria is well known. Lately *Novak* and *Porges* have discovered a tendency toward ketonuria. The cause of these metabolic alterations is seen by most of the authors cited in a disturbance of the function of the liver, from which they have inferred degenerative processes in that organ. It would, however, be remarkable if a physiological process such as pregnancy should regularly lead to such severe disturbances; I would regard as the cause of these metabolic disturbances only an increase in the irritability of the liver, which is a partial phenomena of the increased vitality of the whole organism.

It is very noteworthy that numerous symptoms point to an increased function of almost the whole ductless glandular system. Certain of the previously mentioned symptoms may be referred with a certain probability to an energetic activity of the chromaffin tissue; the regular occurrence of iron-free pigment perhaps points also to an increased adrenalin consumption.[1] As is known such pigmentations develop along the linea alba, at the navel, on the perineum, on the labia majora, on the areolæ of the nipples, and on the face (chloasma uterinum). Very noteworthy is the occurrence of abnormal hairiness, as *Halban* first pointed out. Especially distinct is the increased growth of a previously existing rudiment of the beard. *Halban* cites a very interesting case of *Slocum's*. A woman carried three children normally and also had an abortion at the sixth or eighth week. In each pregnancy the beard grew on the cheeks and chin. But also the downy hair on the entire body, especially on the abdomen and on the linea alba, grew stronger during pregnancy. These hairs fell out again after the labor. *Halban* could even demonstrate the increased growth tendencies of the hair in animal experiment. After shaving of the abdomina of pregnant animals the hairs grow faster there than on the abdomina of nonpregnant animals similarly treated. He refers these anomalies in the hairiness to the internal secretory activity of the chorionic epithelium; it would also be likely, however, that this comes into relationship with the hyperplasia of the suprarenal cortex that occurs in pregnancy, as is pointed out by *Glynn*. This hyperplasia of the suprarenal glands has been demonstrated by *v. Haberer* and *Stoerck*.

I would attribute especial value to the fact that during pregnancy the interstitial glands develop enormously. This fact shows that also in the sexual glands of the female there is a certain independence of the function of the interstitial glands from that of the generative glands. While the activity of the follicular apparatus becomes inhibited, the interstitial glands show histological signs of an increased activity. According to my view the clinical symptoms correspond to those of the histological finding. As I already emphasized in the article on ductless gland diseases in *Mohr-Staehelin's* handbook (Vol. IV), I cannot subscribe to the opinion upheld especially by *Tandler* and *Grosz* that during pregnancy the "internal secretory" activity of the ovary is inhibited by the persistence of the corpus luteum. By "internal secretory" activity is understood by these authors a function that in fact can only depend on the interstitial glands. Against an inhibition of the interstitial glands speaks, however, the fact that during pregnancy the secondary sexual characters throughout do not retrogress, and on the contrary there is found, in agreement with histological findings a strong accentuation of them. Entirely especial, however, are the views concerning the relation of the sexual glands to the hypophysis, which had led to the rapid entrance into the literature of what I consider an incorrect view. Therefore I must enter into this question more in detail.

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[1] Confer the hypothesis as to the genesis of the pigmentation in the chapter on the suprarenal apparatus.

The hypophysis in woman during pregnancy enlarges considerably. Its weight can rise to two and one-half times as much as normal. Enlargement of the anterior lobes is exclusively responsible for this increase in weight; this lobe becomes more juicy and essentially softer. It shows the occurrence of enormous numbers of pregnancy cells, that develop from the so-called chief-cells. In the later stages of pregnancy more than four-fifths of the organ may consist of the new formed cells. *Comte*, *Launois* and *Moulon* first pointed out this enlargement of the hypophysis, and *Erdheim* and *Stumme*, whose exposition I follow, carefully studied these alterations in a great number of cases. Then enlargement of the hypophysis during pregnancy is sometimes so considerable that in rare cases even a pressure-action on the chiasma seems to be possible. *v. Reuss* described repeated temporary blindness during pregnancy, while *Bellinzona* and *Tritondani* report on bilateral narrowing of the visual field. Actually there exist a series of manifestations that point to an increase in function of the hypophysis during pregnancy. To these may belong the osteophyte formations on the internal surface of the skull that are associated with marked hyperemia of the dura. In addition they are found also on the upper jaw, on the nose, and on the frontal and parietal bones (*Manau*), further the development of substance devoid of calcium in the pelvis. *Breus* and *Kolisko* determined increase of the growth of the pelvis during pregnancy. *Tandler* and *Grosz* point out that in gravid persons there is a coarsening of the facial features, especially of the soft parts of the nose, lips, and moreover that a thickening of the hands is not rare, manifestations that remind one of a slight grade of acromegaly. I refer in the chapter on the hypophysis to the case of *Marek*, in which we can indeed speak of a transitory forme fruste of acromegaly. As far as the growth of hair on the linea alba is concerned, I should rather ascribe it to the hyperplastic alterations of the suprarenal cortex. Into association with increase of function of the hypophysis may be brought also the observation of *Halban* that in youthful persons whose epiphysial junctures are not yet fully closed, the growth can proceed in fits and starts during pregnancy. I shall refer to this later.

We see therefore that in pregnancy an increase of the function of the hypophysis is associated with an increase of function of the interstitial glands, as is also the case in acromegaly. There remains only one point that also seems very much to support the view of *Tandler* and *Grosz*. *Tandler* and *Grosz* concerned themselves with the observation that the extirpation of the ovaries, hence a removal of the internal secretory activity of these organs, leads to enlargement of the hypophysis, and they thus regard the cause of the tall growth in the castrated to an increase in the function of the hypophysis. *Fischer* first reported that in capons and castrated male cattle the hypophysis is often twice as large as in cocks and uncastrated male cattle. Moreover, *Jutaka Kon* states that in eight castrated women the hypophysis was found enlarged and rather heavy. The enlargement affected the glandular part alone and on histological examination there was found the picture of true hypertrophy. Finally *Tandler* and *Grosz* several times observed a strikingly large sella turcica in "skopzen." So far as the findings in the hypophyses of castrated animals is concerned, there is found, however, the statement that manifestations of an apparently degenerative kind (vacuole formation) are often observed. I exercise great scepsis with regard to the finding of *Jutaka Kon.* At least one cannot draw from it the inference as to an increase of function of the hypophysis, for nobody would state that symptoms occur in castrated women that indicate such an increase. In male late castrates may be observed such as enlargement of the sella turcica, as in one of the cases I reported (castration in the twenty-sixth year of life), or in the case of *Rieger* (epistolatory communication). Further *Tandler* and *Grosz* have already stated that no enlargement of the sella was found, and further on I shall report four cases of eunuchoidism, in which the sella was found to be normal in size or strikingly small. Finally as far as the tallness of eunuchs and eunuchoids is concerned, I would refer it not to an increase in function of the hypophysis, but to a persistence of the epiphysial junctures. As we have seen in the chapter on the hypophysis early acromegaly does not always lead to tallness, also not when the epiphysial junctures have not closed prematurely. Nor are there to be found in eunuchs or in eunuchoids any other signs of a hyperfunction or an increased function of the hypophysis; I call to mind only the so characteristic behavior of the carbohydrate metabolism in acromegaly. The view of *Launois* and *Roy* that when the epiphysial junctures are open, functional increase of the hypophysis leads to tallness or to gigantism, and when closed, to acromegaly is to my mind as untenable as the opinion that falling away of the sexual glands produces increase of function of the hypophysis. If we follow both views to their ultimate consequences, we arrive at the postulate that castration after epiphysial closure must call forth acromegalic manifestations, as is evidently not the case. And I believe therefore that *Halban's* symptom of increase of growth in youthful gravida does not depend so much on increase of hypophysial function but rather much more on the periodically increased vitality of the whole organism when the epiphysial junctures are open.

Let us now return to the behavior of the ductless glandular apparatus in pregnancy. I must here mention the fact known already in antiquity that during pregnancy there is increase in volume of the thyroid gland. There develops a parenchymatous struma that feels soft on palpation. There is indeed no doubt that this increase in volume is associated with a slight increase in function, that is even a partial phenomenon of the increased vitality.

An increase of function of the parathyroids and of the pancreas can be inferred by us only indirectly, from the fact that the latent insufficiency of these glands tends to be manifest during this period; we have grounds for assuming that this occurs as a consequence of increased demands and therefore that normally the function of these ductless glands is increased.

We will now describe the changes undergone during pregnancy by the *mammary glands*. First of all I will make some remarks as to their development. *Halban*, whose important works we have to thank for our information, distinguishes four periods of growth impulse separated in point of time. The first falls about in the time between the eighth and ninth lunar months. The second occurs at the time of puberty, the third always recurs at the premenstrual periods, and the fourth, especially intensive, occurs during pregnancy. The ovaries constitute the trophic center for the first three growth impulses. This may already be seen by the fact that in disturbances in the development of the ovaries the breasts too remain undeveloped *(Foges)*. The growth impulse during puberty leads as is known to a noticeable development of the glandular parenchyma. The growth impulse in the premenstrual periods can in rare cases be so strong that in virginal individuals colostrum may be secreted, and later, during the menstruation, milk may appear (*Scanzonis Gauthier*). The most intensive impulse of growth occurs during pregnancy. The breasts swell and toward the end of pregnancy may yield colostrum on expression. There is no doubt but that this impulse for growth is set free by hormones. This is shown by observations on the Siamese twins (*Blazek*); when the one became pregnant the breasts of the other swelled also, and after confinement, secretion of milk occurred in both (*Schauta*); *Grigori* and *M. Cristea* could make the same observation on parabiotic animals. For the hormone theory speaks also the observation of *Ribbert* that transplanted mammæ secrete milk after birth. The ovaries are not necessary for the pregnancy-hyperplasia of the mammæ, as also in spite of castration undertaken in the early stages of pregnancy, the development of the breasts proceeds in a normal manner, and the women are able to suckle their children. *Mainzer* has collected sixteen such cases from the literature and *Halban* has added three more. It looks very much now as though the removal of the ovary later exercises a favorable influence on milk-production, as breeders state that castrated cows yield abundant milk. Noteworthy in this respect is the case of *Foges*. After a labor a woman experienced a secretion of milk for seventeen years. During this time constant amenorrhea existed. After seventeen years menstruation a new conception occurred. After the labor the milk-secretion continued again for six years.

Milk usually comes on two or four days after labor. This whether the birth takes place at normal time or whether there has been a miscarriage. Secretion of milk has even been observed after an abortion as early as the second month of pregnancy. As the pregnancy-hyperplasia of the breasts is independent of the ovaries, *Starling* and *Lane-Claypon* have regarded the fetus as the source of the mammary gland hormone. Actually they even succeeded in inducing growth of the mammary glands by injection of extract of embryos into the peritoneal cavity of rabbits that had not yet been covered. Also *Biedl* and *Königstein* lend themselves to this view, as has also *Foá* who recently on the ground of his experiment has upheld the opinion that the mammary glandular hormone was not specific in kind. Against this *Halban* has upheld the view that the pregnancy-hyperplasia of the breasts is produced by a hormone, that proceeds from the chorionic epithelium of the placenta. *Halban* bases his view on the following observations. The pregnancy-hyperplasia of the breasts can still develop if the fetus has been dead a long time but the placenta remains living. If, however, the placenta too dies, the further development of the mammary glands ceases and milk begins to flow. *Halban* further observed two cases of cystic mole, in which secretion of milk began after expulsion of the mole. *Halban* sets forth that the chorionic villi develop from the fertilized egg and in spite of enormous growth until the end of pregnancy undergo but little differentiation. By the copulation of spermatozoa and ovum is explained the fact that the hormonopoietic action of chorionic epithelium is stronger than that of the ovum alone. Hardly anything can be objected against *Halban's* clinical observations. On the contrary it seems to be not refuted that also from the fetus may mammary glandular hormones proceed, as indeed the chorionic epithelium may live without fetus, but not the fetus without chorionic epithelium. Hence it seems to me that the views of *Halban* and of *Starling* are not irreconcilable.

Yet a few remarks concerning the onflow [“Einschiessen,” literally a shooting in of the milk] which, as previously mentioned, usually occurs on the second to fourth day after birth. It was formerly regarded that the cause of the onflow was the act of suckling, but *Halban* has pointed out that suckling during pregnancy may indeed induce the secretion of colostrum, but never calls forth the production of milk (cases of *Duval* and of *Hildebrand*). The onflow of milk also occurs in cases in which the child has never been put to the breast. On the other hand (apart from such cases as the case of *Foges* cited above) the act of suckling or of drawing off the milk is requisite for the continuance of the milk-secretion. From a series of clinical observations *Halban* draws the conclusion that the onflow of milk always coincides with the removal or the death of the placenta. Also the extirpation of the ovaries at a time other than during pregnancy may increase the existing secretion of milk, while, as is known, the occurrence of menstruation during lactation inhibits the secretion of milk, and indeed in the premenstrual period, and also that amount of its solid constituents, especially the casein, the fat, and the salts, are diminished (*N. Davis*). Indeed even at the beginning of the climacteric there may exist for a time with the introduction of the ovarian function painful swelling of the breasts and excretion of milk. *Halban* reports such a case. *Halban* therefore concludes that the ovary is growth-inducing and secretion-inhibitory on the mammary glands, just as is the placenta, only less so.

Finally there remains to be mentioned the pregnancy reactions of the fetus described by *Halban*. The uteri of new-born girls regularly show considerable hyperemia and histological alterations of the mucous membrane that bear great similarity to those of menstruation. There may even occur genital hemorrhage, that have nothing to do with menstruatio præcox, as the latter usually set in much later, at a time that ovaries have shown signs of maturity. The uterus of the new-born girls shows almost always a slight involution that is usually completed three weeks postpartum. Moreover, the mammary glands of new-born girls and boys show signs of epithelial proliferation, indeed, even the secretion of colostrum (witch's milk). Further, the blood shows a slight grade of hyperleucocytosis and increased coagulability. Finally the prostate of the new-born boy shows a slight hyperplasia, which is then affected by involution. *Halban* correctly brings all these manifestations in analogy with the pregnancy-reactions and ascribes them to the hormonopoietic function of the chorionic epithelium.

After labor, as is known, there occurs in the mother a rapid retrogression of all the profound alterations just described. The neutrophilic hyperleucocytoses give place to a leucopenia with mononucleosis, the tachycardia temporarily to a bradycardia. With the onset of the milk, numerous eosinophilic cells make their appearance in the blood (*Blumental*). According to *Novak* and *Jetter* there are found in the early puerperium different irritative symptoms of the entire vegetative system; then the signs of an increase in the functions of the ductless glandular system gradually vanish.

Surveying now the alterations described, that take place in the organism of pregnant women, we find that they are entirely analogous to those that occur in the premenstrual period, while those of the puerperium are analogous to those of the menstrual period. As is known, labor takes place at the menstrual term. Hence seems justified the dictum of *W. H. Freund* that "labor is a menstruation, in which a fully developed egg is extruded." While, however, the phenomena of the premenstrual period proceed from the ovary, there can be no doubt at all that the similar, but potentized, manifestations of pregnancy proceed from the developed egg. It therefore seems to me that the conclusion lies at hand that all the manifestations of premenstrual period are set free by the maturing follicle, which only renders intelligible the fact that the extirpation of the ovaries during pregnancy has no influence on this phenomenon, as the maturing ovum no longer is found in the ovary, but in the uterus. From this we see that if we ascribe to women an interstitial gland, it can have very little to do with the phenomenon during pregnancy. It takes part in hyperplasia and in increase in function only in the same manner as do the other ductless glands, and the stronger emphasis of many of the so-called sexual characters may stand in connection with it. The most important prevailing alterations of pregnancy are at all events independent of it.

At the *climacteric* the interstitial glands show certain regressive changes; they are, however, retained in part, while ovulation ceases entirely. The lipoidemias that *Neumann* and *Hermann* observed in postclimacteric women are in my opinion to be referred to the falling out of the function of the follicular apparatus. As is known, libido may be retained for a still longer time. The function of the sexual glands is usually associated with an increase in the fatty layer of the abdomen and mammæ. As is known there occur during the transition period numerous nervous disturbances, that point to extraordinarily changing and manifold conditions of excitation in the vegetative nerves. Manifold symptoms of a psychical hyperirritability are added, an existing hysteria becomes worse, and when a predisposition to a psychosis exists this may develop to a climacteric psychosis, which, however, has no specific character (*Krafft-Ebing*).

We now have to consider the question as to whether the generative apparatus in man too possesses an internal secretion. We have already seen that there are clinical observations to the effect that the function of the generative apparatus does not develop (the kryptochides inguinales of *Variot*), while the interstitial glands and with them also the masculine habitus are well developed, and that on the other hand similar results have been brought about by experiments. It would now be proper to investigate whether such sterile but otherwise masculine individuals possess the same libido as normal individuals. The cardinal point is the fact whether the developmental disturbance sets in in early youth, or that experimental attack is made on quite young animals. For experience teaches that if once the generative apparatus has been fully developed and has functionated normally that also after complete extirpation of the sexual glands the libido can be retained for a long time. It seems to me important, however, that also in such cases the libido is mostly released only through external influences. On the whole it seems to me, although I can not demonstrate this with certainty, that a normally strong sexual instinct is present only when the function of the generative gland is normal, and in this circumstance speaks for the hormonopoietic function of the generative glands.

The known stimulating action on the central nervous system, which expresses itself in tendency to movement and in a heightened muscular tonus, which comes to expression also in a spiritual sense in higher creative activities and which characterizes especially the period of "Sturm and Drang," I would refer more to the hormonopoietic activity of the generative glands. What has been done experimentally on this question does not lend itself to the support of this view. On the whole the numerous reports as to the stimulating action of testicular extract and of spermin *Poehl* have not been carried with the necessary critique; the careful investigations of *Zoth* and *Pregl*, that showed an increase of the muscular capacity, were made with extracts of whole testicle, so we are unable to say what part the generative glands had in producing the effect.

While in man the function of the generative glands is a more continuous one, there exist in the most of male animals the same cycle as in the females. As is known, the complete extirpation of the sexual glands prevents a recurrence of rut. Although in some cases the wave of rut remains for some time longer, I would not lay much stress on this fact as *Halban* does. Here also must we consider that the organism had been accustomed to the rut-wave for a long time. As certain cohabitation experiments show, however, it is possible that it is promoted psychically by the rutting female. I believe also here the question permits of discussion as to whether many of the rut phenomena usually grouped with secondary sexual characters, that are necessary for the act of copulation, as for instance, the hypertrophy of the arm musculature and the thumb callosities in frogs, are set free by the generative glands. I have been unable to find any experimental investigations that help to clear up this question.

## I. THE MALFORMATIONS

It is not my intention to enter into a comprehensive exposition of the malformations accruing to the sexual glands. I shall only choose those types that seem to me important for the discussions of the problems stated above.

### I. Aplasia of the Sexual Glands

*Halban* has collected from the literature the reports of cases of congenital amorphia or aplasia of the ovaries. They all come from the older literature, so that *Tandler* and *others* have expressed doubt as to the exactness of the observations. It is true that this doubt does not extend to the observations on anorchia that were made on boys shortly after birth. In such cases are always found also anomalies of the internal genitalia—anomalies such as lack of the epididymis or of the funiculi spermatici or the vesiculæ seminales. When, however, we hear in many of the observations in old literature as to aplasia of the sexual glands that the external and internal genitalia were quite well developed, or that in the male individual a beard was present, such a doubt is well justified. It is at all events very striking that no such observations have been made in the last decade, although the number of sections has enormously increased. From the observations on anorchia in new-born children the most that can be mentioned is that also without sexual glands there is possible a development, if only a disturbed development, of the male or female accessory genital apparatus, and perhaps other characteristics of the male sex.

Also the observations that *Landau* and *Peck* publish concerning the existence of individuals of a neutral sex do not seem to me to be free from objections. I quote the following two cases that *Peck* regarded as especially important. In the case of *v. Swinarski-Pfannenstiel* there was a fifty-five-year-old unmarried "woman," who had never menstruated. The general habitus was masculine, the clitoris 3 cm. long, both ovaries were considerably enlarged, the superficies smooth, no corpora lutea were to be seen, and on microscopical examination the ovaries were found to be entirely "parenchymaless." The internal genitalia were those of the female. The case of *Howitz* was that of a forty-nine-year-old unmarried "woman." The hairiness and form of the pelvis were masculine; the large and small labia were present, the clitoris was 6 cm. long and 2 cm. thick. The urogenital sinus was smooth and on its floor was found an opening through which one could pass a thin sound into the 7 cm. long vagina. Between the thirtieth and fortieth years of life blood issued from the vagina at intervals of one to several years. At the site of the ovaries on each side was to be found a body of the shape and size ot an almond. There was no follicle formation in the ovaries, and the stroma was strikingly hard. In this case that had come to advanced age one could not say with certainty that the follicular apparatus had always been entirely absent. The absence of menstruation does not allow of the statement that at least for a time there did not exist a tendency [start, Ansätz] for menstruation. Also statements to the proportioning of the body are not given. Finally an examination of the suprarenal cortex in such cases would be very desirable. It seems to me therefore that such cases should not enter into our discussion.

## 2. Hermaphroditism

We distinguish a *hermaphroditismus verus* and *hermaphroditismus spurius* or *pseudohermaphroditism.* Cases of hermaphroditismus verus, in which ovaries as well as testicles are capable of functionating, are as yet unknown in man. But there are cases of so-called ovotestis; I will cite some examples. A case of *Salén* was that of a forty-three-year-old "woman." Menstruation had existed since the seventeenth year, the clitoris was 5 cm. long, the vagina 6 cm. long, the labia majora were of normal development, the habitus was feminine. The ovotestes show in the ovarian part *Graafian* follicles and typical ovula, in the testicular part seminal tubules, *Leidig's* interstitial cells, but no sperm. The case of *Simon* was that of a twenty-year-old "man." The individual felt as if he were a man. The sexual inclination was masculine. Menstruation had existed for three years, the secondary sexual characters were mixed, with the feminine predominant. The labia majora were well developed, the penis was 6.5 cm. long, the glans was not perforated. There were found tubes, parovaries, and ligamenta lata; vasa deferentia and epididymis were without connection with the testicular part of the ovatestis. In the latter were found typical sexual glandular tissue of both sexes, but no sure signs of function.

In pseudohermaphroditism there are found sexual glands of one sex and the sexual characters of the other. We distinguish *pseudohermaphroditismus internus*, if only the internal sexual passages of the other sex are present, and a *pseudohermaphroditismus externus*, if only the external sexual passages of the opposite sex are present, and a *pseudohermaphroditismus completus* when both external and internal sexual passages of the other sex are present. Further, according to the prevalence of the sexual glands a *pseudohermaphroditismus femininus* or *masculinus*.

As an example of the pseudohermaphroditismus completus I cite the case of *Heyn*. The habitus of a forty-six-year-old individual was entirely feminine. The person married at the age of twenty-one years, sexual intercourse was entirely normal and was attended with orgasm and discharge. There was found a vaginal cul-de-sac; uterus, ovaries, prostate were absent. Testicles were present on both sides.

In pseudohermaphroditism are found all conceivable varieties. There are cases of somatic pseudohermaphroditism in which not only the sexual organs but all the psychical characteristics of the other sex prevail. *v. Neugebauer* has collected twenty-five such cases. Further, there are cases in which the secondary sexual characters, such as hairiness, voice, dimensioning of the body, belong partly to one and partly to the other sex, and there are cases in which the sexual glands and genitalia belong to one, the secondary sexual characters to the other sex (pseudohermaphroditismus *secondarius*, *Halban*).

Finally there are observations concerning *unilateral pseudohermaphroditism*. In man so far as is known, this has been observed in a very rudimentary form only. *Halban* cites cases of unilateral development of the breasts in women. There are, however, numerous such observations on the part of zoologists. *Delbet* saw butterflies that possessed on the one side an ovary, and on the other a testicle, and in which one-half of the body was colored like that of a female, the other side like that of a male. I further cite the known observation of *Weber*. A finch possessed testicle and male plumage on one side, an ovary and female plumage on the other.

Let us now survey the rich material of facts, from which I have chosen only a relatively few illustrative examples, but examples that are important, and let us proceed on the basis of these to enter into the discussion of the problems mentioned above.

Let us turn first to the relation between sexual glands and the secondary sexual characters. I would here sketch again, in outlines, the different views. We have seen that in this respect two views stand bluntly opposed to each other. According to one the sexual characters exist from the beginning, there exists a male, a female, and hermaphroditic predisposition, and the sexual glands exercise only a protective stimulus on the development of the sexual characters. According to the other, it is the sexual glands alone that form the sexual characters. The authors that adhere to the last opinion, show that indeed already in the first embryonal stages there are differences to be observed between the male and female sex, but that the sexual glands have begun to develop already at this time and begin to exercise their influence.

It will be seen at the first glance that multiplicity of the phenomena is not explained in a satisfactory manner by the last-named assumption. How shall we explain the coming about of complete hermaphroditism in which the sexual glands of one sex lead to the development of the sexual characters of the other, if the sexual glands exert a specific sex-determining formative stimulus? Even less explicable according to this hypothesis is the occurrence of unilateral hermaphroditism. In this connection, no matter from which point of view we regard the matter, we cannot circumvent the opinion of *Halban*. For this opinion speaks also circumstance that in hermaphroditism the heterosexual characters are enormously developed even at the time of puberty, and the known fact that unioval twins are always of the same sex. Only in the last analysis does this solution meet with great difficulties. According to it we should suppose that the protective influence of the sexual glands would be always active if it met with a heterosexual predisposition. According to this we would expect that when the sexual glands are extirpated in a not yet fully developed animal, and the sexual glands of the opposite sex are implanted in this animal, the original predisposition would come to development even then. *Steinach* has followed this method. He implanted ovaries into previously castrated young males of guinea-pigs and rats. The transplants "took" and not only the interstitial glands developed but also the primary follicles, to large follicles with normal ova, and there occurred in entirely normal manner the formation of atretic follicles of corpora lutea. In these animals not only did the penis cease development, but it was even set back in its development. If a tube and a piece of the uterus were transplanted with the ovary, these developed to mature organs. Moreover, there came about an enormous development of the mammary glands, that in form and size were entirely like those of normal female, and indeed even exceeded them in size. Moreover the animals remained behind in growth, the body showed entirely the proportioning of the female; also the growth of hairs and the layer of fat showed the texture of that of the females, and there was a reversal of the psychical sexual characters.

If *Steinach's* experiments were to receive full corroboration, were someone in converse manner successful in bringing to previously castrated females the male sexual characters by implantation of testicles, we would have to agree that they would stand in contradiction to *Halban's* view. I believe, however, that we would not overlook the difficulty of the problem, if we were to regard the problem as entirely solved by this view; for *Steinach's* experiments do not explain the occurrence of heterosexual characters in the presence of the sexual glands of the other sex. The observations belonging to this problem have led *Biedl* to assume an hermaphroditic mapping-out [Anlage] of the sexual glands. The occurrence of heterogenous sexual characters is explained by *Biedl* by his supposing that the internal secretory part of the sexual glands that belongs to the opposite sex gains the upper hand. *Biedl* thus explains the occurrence of certain masculine characters in old women after the menopause.

On cessation of the activity of the female sexual glands, can there, according to *Biedl*, occur a reversal of the sexual characters in that the existent male sexual glands continue to functionate. I would here agree with *Novak* in not considering the illustration that *Biedl* employs as convincing. The occurrence of the so-called old woman's beard is not a male sexual character. Its occurrence is explained much more to the purpose by *Halban*, who points out that the individual sexual characters possess very different tendencies to growth and that the development of the beard in women is very much delayed. In the same manner I do not regard the localization of the deposits of fat in old men as a female sexual character, but rather as the sign of the beginning dissolution of the activities of the sexual glands, only as the suggestion of a symptom that in eunuchoidism is exhibited in early years in a pronounced manner.

It therefore seems to me that the only possibility is to seek for the solution of the problem in another direction; in that we should not endeavor to crowd all of the manifestations into one of the views set forth, but should consider the question as to whether the genesis of the sexual characters is not determined by a number of factors. We cannot discard the assumption of a preexistent tendency for certain sexual characters without doing away with the problem altogether. Before all, however, we should think of the possibility that the sexual glands actually give off the formative stimulus for many a sexual character, especially if we take the viewpoint that some of the sexual characters come under the dominating influence of the interstitial glands, others under those of the generative glands. I have previously set forth that if we ascribe to women an independent function of the interstitial and the generative glands, the development of the mammary glands seems to stand only under the formative stimulus of the follicular apparatus or of the ovum. From this standpoint it is worthy of note that *Steinach* in his experiments transplanted not only the interstitial glands but also the follicular apparatus. We can readily imagine that the interstitial glands alike whether they come from man or woman, exercise the same protective stimulus on certain preexistent masculine or feminine sexual characters; but no one would expect the same action from the masculine as from the feminine generative glands.

Finally we should think of the possibility that the development of many of the sexual characters comes entirely or partially under the influence of other ductless glands. A new viewpoint has lately opened in this direction, a viewpoint that also seems adapted for showing the occurrence of many a heterosexual character in a new light. I refer to those observations that were described in detail in the consideration of tumors of the suprarenal cortex. Women who have developed entirely normally up to or beyond the age of puberty become, on the development of such a tumor, amenorrheic; the uterus atrophies, and there develops a hypertrichosis. Mustache and beard grow as well as abundance of hairs on the trunk; in short, the distribution of hair assumes quite the masculine type. The supposition that this heterosexual hirsuties is to be referred to a hyperfunction of the suprarenal cortex is very probable, suggesting the thought that also in the virile type of hairiness that is observed in acromegalic women or even in normal women during pregnancy there is the same cause—for hyperplasia of the suprarenal cortex is observed in both conditions.

Why, however, is found, in those cases in which the suprarenal tumor develops in earliest youth, a premature development of the genitalia with marked accentuation of the sexual characters without reversal to the heterosexual type, while, when it occurs in women who are already matured, the activity of the sexual glands fails? In explaining this fact I would refer once more to the relations in acromegaly. Here, in addition to marked accentuation of many sexual characters, in addition to the masculine type, we find either, mostly only temporary, increase of the activity of the generative gland (even with secretion of colostrum) or, what is more frequently the case, the failure of this from the beginning. In this there seems to me to lie an analogy with the behavior of the generative glands in tumors of the suprarenal cortex; we may assume that hyperfunction of the suprarenal cortex always leads to a marked development of the hirsuties on the trunk, but that an increase of the activity of the generative glands enters in only when there is an especial vitality of these glands, while in the cases in which vitality fails, there is rapid exhaustion. In the very strong impulses in childhood there would come about a pronounced increase (premature development) and in already matured individuals an exhaustion. In acromegaly, in which this impulse is very much less feeble, there may occur also in late years first a temporary increase of function, although in most cases the exhaustion appears in the foreground already from the beginning.

These observations and convictions ascribe to the suprarenal cortex an important trophic influence on a very important sexual character, namely, the hairiness. This supposition finds a certain support in embryology and histology. Let us recollect that the suprarenal glands as well as the interstitial glands are of mesodermal origin and that both proceed from immediately contiguous parts of the celom, and moreover that the histological picture of cortical cells and the interstitial cells present a great similarity. Also *Glynn* inclines to the assumption that the suprarenal cortex is a trophic center for the growth of beard and the hairiness on the body, and believes that we should properly expect that in man the suprarenal cortex is better developed than in woman. As is known, this is really not the case. I would not, however, ascribe any great significance to this. As we cannot quite discard the assumption of a masculine or a feminine predisposition [Anlage] for the body, it is explicable that with normal impulses the masculine or feminine type of hair distribution will exist. When, however, the impulse is considerably increased, then the virile type in man is potentized, while in women the virile type is approached or attained. Even under physiological conditions, namely, in pregnancy, is there an approach to the virile type. This idea also includes the explanation of why in pseudohermaphroditismus femininus the suprarenal cortex is usually found so hyperplastic.

## II. AGENITALISM OR HYPOGENITALISM

### 1. The Eunuchs

**Occurrence.**—The manifestations of agenitalism or hypogenitalism occur in the form of a pure physiological experiment in eunuchs and in skopzen. Castration, as is known, was very much practised in antiquity; even until a short time ago it was carried out in Italy for "musical purposes," and in the Orient it is to-day carried out on the watchers of the harem, and in Russia on the religious sect, the skopzen, on religious grounds. All these forms affect male individuals. As to castration of females there exists only a very inexact report from India by *Roberts*.

**Symptomatology.**—An excellent exposition of the symptomatology has been given by *Tandler* and *Grosz*, which I shall in great part follow. The action of castration is different according to whether it has been done in early youth or after the entrance of puberty.

We shall first pay attention to the manifestations of loss of sexual glands in *males*. When the castration occurred in earliest youth, the development of the accessory genital apparatus is extremely deficient. Penis, prostate, and seminal vesicles remain small (*Pelikan*). When castration has taken place in later years the penis becomes only slightly smaller, while the prostate shrinks to a greater extent. As is known, castration has been done for prostatic hypertrophy; I shall consider in detail later on the action of late castration.

In early castration all sexual instinct is absent, and the small penis that remains never becomes erect. As the castration is not always complete, it may happen some of the eunuchs may still experience a slight degree of libido, on account of which some of the harem-watchers in the Orient had their penis removed with the testicles. *A. Marie* reports the case of a forty-year-old Egyptian eunuch who had been castrated in childhood, but who showed illusory ideas that had an erotic content.

If castration has been carried out after development of puberty the sexual instinct—*Möbius* calls it the cerebral sexual instinct—is retained for a long time; copulation is still possible and there occurs an ejaculation of prostatic secretion.

According to *Gall*, the cerebellum should atrophy, and indeed in unilateral castrates the opposite half of the cerebellum. This statement has met with contradiction, although *Möbius* pointed out that no certain contradictory evidence has been advanced. According to a personal communication of *Prof. Tandler*, however, the statement of *Gall* is certainly not in accordance with fact.

The statement as to the characters of castrated individuals varies very much. For the most part it is stated that castrates lack the courage, the passions, and the aspiration of a normal man; they are described as tricky, revengeful, and cruel. On the contrary the intellectual capabilities are not diminished, as many eunuchs have attained to influential positions. It is hard to judge these statements, as in the most of the famous eunuchs, the history lacks exact knowledge as to the time and the completeness of the castration. *Möbius* points out that castrates lack the higher artistic endowments, as the virtuosity of castrated singers cannot be regarded as such. At any rate, animal experimentation shows that castrated animals (oxen, geldings, capons) lack the courage, the animation, and passions of normal male animals.

Noteworthy is the influence of castration on the skeletal formation and the development of the secondary sexual characters. Castration in early years leads in man and animals to increase in length (*Godard*, *Pelikan*, *Pittard*, *Becker*, *Lortet*, *Pirsche*, *Sellheim*, *Tandler* and *Grosz*, and *others*). Eunuchs of 200 cm. in height are observed often. The tallness first sets in at the time of puberty. The closure of the epiphyses is delayed. Many epiphysial junctures may remain open until a high age. Also the ossification of the cranial sutures is delayed. Signs of the frontal, cranial, sagittal and lumboid sutures are retained for a long time. Therewith the skeleton shows especial characteristics; the head is small, the tabular part of the occipital bone is, according to *Gall*, flattened. The spinal column is especially short, the extremities are lengthened, especially in their distal parts, thus causing a certain preponderance of the lower length over the upper length and a relatively large span width. Often the genu valgum position exists. The breadth of the shoulders is diminished, the pelvis shows a mid-form between masculine and feminine type, and remains infantile. In the same cases the sella turcica is found remarkably large. I have already remarked I cannot infer from this an increase in function of the hypophysis. In the tall eunuchoids the sella turcica, as we shall see later, is not enlarged, but rather smaller. The larynx remains small, does not ossify, shows childish dimensions, in which the laminæ thyroidiæ encroach upon each other at a wide angle and the prominentia laryngea is indistinct; the voice does not change, and the childish soprano is retained. The bones, especially the long tubular bones remain delicate, and the sites of the muscular insertions are only very feebly developed. The tonus of the muscles is slight, the phenomena of movement should take place more slowly. The muscles are permeated with fat. The metabolism of the muscles must become essentially altered through the castration, as on castration the meat of male animals takes on the characteristic odor, an experience that is extensively made use of by breeders.

The *skin* is strikingly delicate and pale and in older castrates shows the fawn-yellow coloration and wrinkling. It is very poor in pigment. The *distribution of fat* is very characteristic, fully corresponding to that which will be described under dystrophia adiposo-genitalis. Hence there are found pads of fat in the hypogastric region, and on the mons Veneris, the latter of which is bounded above by a horizontal fold; also on the nates, on the hips and thighs, on the mammary glands and laterally on the upper eyelids that may hang down like bags. In many cases there occurs pronounced adiposity. *Tandler* and *Grosz* distinguish between a tall and a fat eunuch type, although in the first the characteristic distribution of fat is always indicated. The muscle meat is, as in the castrated animals, permeated with fat. The tonus of the musculature is slight.

Finally the *secondary sexual characters are deficient.* While the hair of the head is dense, such individuals are beardless, and show only lanugo hairs on the face, especially on the chin and the upper lip; in later life, individual bristly hairs may develop, similar to those that grow in old women, on the lateral parts of the upper lips. The trunk remains completely hairless and the axillary hairs are absent or are sparse. The pubic hairs are absent, or consist in only a few sparse hairs at the root of the penis. Also the perineum remains hairless. The involution of the thymus gland is slight.

We know much less concerning the results of castration in the *youthful female organism.* According to the inexact statements of *Roberts* the female castrates grow to be tall, the accessory apparatus of the genitalia remain entirely undeveloped, the secondary sexual characters and the breasts do not develop. With this rather agree the animal experiments of *Hegar, Kehrer* and *others*, and the observation on female eunuchoids that will be mentioned later.

### 2. Late Castrates

Castration in man after the onset of puberty is carried out but very rarely. In the most cases the indication for it is found in tuberculosis of the testicles. Later, in late eunuchoidism, we will learn about the group that depends on a traumatic foundation. As, however, in most of these cases the sexual glands remain behind in the body and are only shrunken. I reckon these cases with late eunuchoidism, as it seems to me of like significance whether the shrinking of the testicle is the result of a traumatic action or of another disease process.

If castration in man takes place at a relatively early age there occurs a pronounced regressive alteration of the genital apparatus, and at least a partial retrogression of certain secondary sexual characters, and finally a distribution of fat that is similar to that of eunuchs. It is remarkable that I was unable to find in the literature an exact description of such a late eunuch. From the older literature I quote that of *Martin:* In war, a piece of shell tore away the penis and testicles of a married man. Soon afterward the man lost his beard and his breasts began to increase in circumference. More frequently is found the statement that on castration in already fully developed individuals a retrogression of an already developed accessory genital apparatus and of the secondary sexual characters does not occur.

A short time ago I was able to observe carefully a suitable case, and I herewith report it:

*Observation XLVII.*—Kr. J., forty-nine years old. Entered the clinic July, 1912. In the eighteenth year of life he had gonorrhea and bilateral orchitis. In the nineteenth year of life he acquired lues. In the twenty-first year of life there began a swelling of the cervical lymphatic glands and at the same time a caries of the lower jaw; the latter continuing three years and disappearing after operative procedure. In the twenty-sixth year of life, both testicles were removed on account of tuberculosis. A year after the operation the patient suffered with cardiac palpitations, that later disappeared. In the thirty-seventh year of life he developed a goiter after a trip to Stiermark, which goiter later receded. For several years he has had attacks of typical bronchial asthma.

Since the castration the patient has gradually gained about 30 kg. The potentia coeundi still exists but coitus is carried out but very rarely; ejaculation takes place, but since the operation libido has been but very slight.

The mustache, which even before was not developed very strongly, has become very much more sparse since the operation, so that there exists on the upper lip only a small strip of sparse hairs, as is seen in the accompanying photograph. The beard on the cheeks is now so sparse that the patient has to shave himself much less frequently than formerly. The hairiness of the mons Veneris is very sparse, it is a little denser at the root of the penis. Here it terminates above in a horizontal hue.

The penis is only 3 cm. long, the foreskin has become too long and, therefore, shows numerous transverse wrinklings. In an erect condition the penis is only 4½ cm. long. The hairiness in the axillæ, on the trunk and on the perineum and on the extremities is entirely absent.

The patient is rather fat, the breasts are pronouncedly rich in fat, and the hypogastric region and the mons Veneris are also rather fat.

The case reported is not entirely free of objections, as it might be supposed that the previous gonorrhea and luetic infection and the tuberculosis may have damaged the sexual glands seriously even before the castration. Nevertheless the statements of the patient that the alterations described took place only after the operation are very precise.

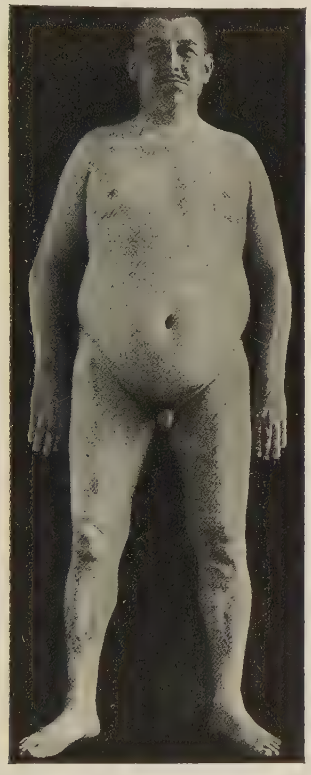

FIG. 66.—Late castrate.

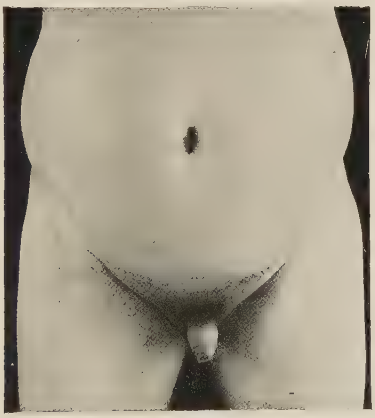

FIG. 67.—Genitalia of a late castrate.

In the female sex castration after puberty has been carried out frequently by the gynecologists. It leads regularly to atrophy of the uterus and vagina. Menstruation remains absent. Also the external genitalia, especially the clitoris, shrink, the vagina becomes narrower. In female animals the sexual instinct ceases. *Bucura* experimented on rabbits. If after the castration the female did not admit the male, this was a sure sign that the operation had succeeded. Also after castration in women is the sexual sense reduced. *Gloevecke* found this in 78 per cent., *Pfister* in 73 per cent., *Alterthum* in 68 per cent. In women who have been having sexual intercourse for a long time, libido may be retained for a while. In rare cases (*Mandl* and *Burger*, *Pfister*) the libido may be increased for a time after the castration.

After the castration the skin becomes lighter on account of loss of pigment (*Pfister*). The hair of the head becomes luxuriant. There is no distinct influence on the shape of the breasts; but the nipples show a slight grade of atrophy, and the areolæ become light rose through partial loss of pigment.

As in man, there is in woman after castration a tendency to corpulency. Considerable increase in weight was found by *Alterthum* in 29.5 per cent., by *Glaevecke* in 57.5 per cent.

The behavior of the respiratory metabolism after castration has become a subject of lively discussion. *Löwy* and *Richter* found in female castrated animals the fundamental exchange lowered about 20 per cent., in the males about 14 per cent. On administration of ovarian substances it again rose to normal. Against this, *Lüthje* has pointed out that the slight reduction of the fundamental exchange was to be referred to the greater phlegma of the animal. *v. Noorden* has subjected the experiments that exist in the literature to a thorough criticism, and comes to the conclusion that a reduction of the fundamental exchange has not as yet been strictly demonstrated. The clinical observation of an increased deposit of fat after castration is ever known "on account of the broad basis on which it rests, unquestionable." Recently further investigations by *L. Zuntz* have been made on three women who were castrated on account of gynecological complaints. During the first week *Zuntz* found no distinct reduction of the fundamental exchange. In all cases there was found, after a long time, a slight fall of the oxygen consumption, as much as 20 per cent. The administration of oophorin was not able to produce a distinct addition to the oxygen consumption. We shall see later that also in eunuchoidism, in the few investigations that have been made up to the present, the respiratory metabolism was found to be rather normal. There is no ground, however, for the fact that the corpulency that develops after castration in a great majority of cases does not depend directly on the loss of the sexual gland, as small turnings of the scale not demonstrable by our present methods may amount to something in the course of years; and as the disturbance in the regulation of the fat metabolism does not depend exclusively on the fundamental exchange (see Chapter XIV).

Very little is known as to the other alterations of the metabolism that occur after castration. Also the action of the sexual glandular substances introduced in the organism has not been sufficiently studied up to the present. As we have seen before, its influence on the respiratory metabolism is still subject to controversy. Many authors (*Matthis*, *Neumann* and *Vas*, and *others*) found under the influence of oophorin a slight increase in the elimination of nitrogen, and an increase of the limitation of salts, especially of the elimination of phosphorus through the intestine.

*Cristofoletti* saw after the administration of ovarian substances the glycosuric action of adrenalin become weaker.

In woman, the acute loss of the sexual glands leads, as is known, to a series of manifold excitatory states of the vegetative nervous system. Drawing pains, emotional excitements, feeling of anxiety, headache, fainting spells, heat and feeling of cold, disturbance of the intestinal tract, weakness of memory, and mental depression occur. The wave-movement ceases. The manifestations become intelligible when we consider what distinct revolutions occur in the female organism after castration.

*Cristofoletti* saw after castration (also in animal experiments) increase of the glycosuric action of adrenalin. *Alder* found delay in the coagulation-time of the blood and reduction of the calcium in the blood.

As is known, all these manifestations occur also at the climacteric. "Castration produces an artificial climax, that is like the natural one, and often transcends it in pathological manifestations" (*W. H. Freund*).

We shall consider the therapy of eunuchism later.

### 3. Eunuchoidism

Dystrophia adiposo-genitalis, gerodermia genito-distrofico, Obésité d'origine genitale.

**Definition.**—*Eunuchoids we term, according to Tandler* and *Grosz, individuals who without being castrated entirely simulate in their clinical manifestations the true eunuch type, or at least are extraordinarily similar to it. They are either tall, or if complications are absent at least not stunted in growth; they show the typical fat distribution of eunuchs, and eventually pronounced obesity; the epiphysial junctures persist abnormally long, the skeletal dimensions are characterized by an especial length of the extremities, and furthermore the individuals show a definite psychical habitus. Finally there is found a more or less pronounced disturbance of development of the genitalia with faulty development of the secondary sexual characters. It is probable that in such cases we have to do with a developmental disturbance beginning primarily in the sexual glands and indeed especially the interstitial glands, as functional disturbances of the generative glands alone do not lead to eunuchoidism.*

**Historical and Case Histories.**—Such a case was first termed eunuchoid by *Griffith.* A sharp delimitation of the clinical picture occurred only a short time ago, when *Tandler* and *Grosz* first reported a series of cases and then described the clinical picture thoroughly. Even before *Tandler* and *Grosz*, however, a great number of such cases had been reported in the literature under very different names.

*Meige* mentions a case of *Reichlin's* that was a pronounced eunuchoid. Moreover *Tandler* and *Grosz* regard as an eunuchoid the case of *Redlich.* Similar cases were described by *Kisch.* *Kisch* distinguishes between hereditary and acquired obesity and divides the hereditary obesity into two forms, one of which develops in early youth and which becomes prominent later and in which only the predisposition to obesity is inherited. Then *Kisch* mentioned that the hereditary obesity "acquires a quite characteristic nutritive expression of degeneration." The description of these types that *Kisch* furnishes suits entirely, as *Tandler* and *Grosz* point out, the eunuchoid type. Among two hundred thirty-eight cases of obesity, *Kisch* saw it twenty-four times and development at an early age seventeen times.

*Pirsche* cites the case of *Papillaunet* and adds three observations of his own. Other cases have been reported by *Etienne*, *Jeandelize* and *Richon* (man fifty-nine years old, 174 cm. tall, preponderance of the lower length, epiphysial junctures incompletely closed, the testicles—one cryptorchiditic—very small and fibrous, seminal vesicles and prostate also small and fibrous, penis 4 cm. long); and by *Duckworth* (thirty-seven-year-old man, 171.7 cm. tall, 179 cm. span width, considerable preponderance of the lower length, marked fibrosis of the testicles, the prostate, and the epididymis (already described by *Griffith*); already *Duckworth* mentions the similarity to "cryptorchid conformation." Very worthy of mention are the cases of *Sainton* of five brothers (and sisters) three were eunuchoids, and besides this an uncle and great-uncle. The case described was 172 cm. tall. The lower length predominated considerably. The thymus gland was not persistent. I believe that also the case of *Babonneix* and *Paisseau* (case I) and that of *Lemos Magalhaes* belong to this group; also the case of *Thibierge* and *Gastinel* (termed gigantism with infantilism).

*Neurath* furnishes the description of an eleven-year-old tall-grown girl with typical "eunuchoid" obesity, that is very likely a case of eunuchoidism.

Also the case of *Porhon* and *Mihaelesco* described by these authors as "cas d'infantilesme dysthyreoidique et dysorchitique" seems to me to belong to this group, as also the case of "anorchidia" of *Launois* and *Roy*.

Also the case of "cryporchides abdominaux" *Variot;* also a case of *Apert*, also case I of *Babonneix* and *Paisseau* would fit in this group very well.

Of especial interest is the case of *Josefson* and *Lundquist* that affected a female eunuchoid, I shall consider this in detail later on. I also mention here briefly the case of *Peritz.*

During the course of the last few years, I have seen four cases, which I shall report, before entering into the description of the symptomatology.

*Observation XLVIII.*—B. Sch., thirteen and one-half years. First observed Nov., 1910. Father had lues at the age of twenty years. His Wassermann still positive. As a child the patient had an umbilical hernia, and a left-sided inguinal hernia, also slight constipation. The umbilical hernia healed three months after birth, the inguinal hernia only after some years, three years ago operation on the tonsils.

Before this, always sore throat and snorings. For about three years gradual onset of obesity. In addition vomiting sometimes, especially after breakfast. When the vomiting has finished, appetite returns. The boy now weighs $55\frac{1}{2}$ kg. The body build is slender. The skin pale, soft, satiny, facial complexion pale, marked collection of fat on the breasts, in the inguinal region and on the mons Veneris. The penis is quite small, as is also the scrotum; the right testicle is about the size of a plum-kernel, the left is about half the size and is not quite descended. Examination of the eyes shows entirely normal relations. *Likewise the X-ray examination of the skull* [*i.e.*, normal]. Sella turcica rather small. Temperature 36.2°, circumference of the head 54 cm.

Erythrocytes, 5,290,000.

Hemoglobin, 95 per cent.

Leucocytes, 10,700, of which:

Polymorphonuclear neutrophiles, 49.6 per cent.

Large mononuclears, 3 per cent.

Lymphocytes, 42.4 per cent.

Eosinophiles, 5 per cent.

Genu valgum on each side.

The boy is well developed mentally, but lazy. He is silent, especially in intercourse with companions of the same age.

Thyroid small, hardly palpable. Liver and spleen not enlarged.

Thyroid gland treatment. Loss of about 3 kg.

June, 1911. The boy has grown, still very fat, typical distribution of fat. The testicles are not better developed. The right testicle has a longitudinal diameter of about 25 mm., the left of about 18 mm., the latter is fully descended.

Leucocytes, 10,800, of which:

Polymorphonuclear neutrophiles, 50.94 per cent.

Lymphocytes, 31.26 per cent.

Large mononuclears, 12.8 per cent.

Eosinophiles, 3 per cent.

Eye examination normal.

Jan., 1912. A new X-ray examination of the skull showed that size of the sella turcica had not essentially altered. The examination by a perimeter showed an entirely normal visual field. The thyroid treatment was tried once more, which, however, soon led to slight signs of hyperthyroidism and hence had to be abandoned. The patient was then ordered radium baths three times a week with 100,000 Mache units per bath, which perhaps exercised a favorable influence. At all events there became apparent a distinct progress of the development, as even the patient thought in June, 1912. The patient was now 174 cm. tall and still somewhat fat. Abundant fat deposits were to be found in the hypogastric region. The pubic hairs were now well grown, but still showed a horizontal boundary above. The trunk was still fully bald, and only in the axillæ on both sides were a few sparse hairs to be seen. The size of the penis and the testicles corresponded to the age of the patient. It was stated that pollutions had not as yet occurred. The voice had changed and the patient complained only very rarely of headaches. Some adenoid vegetations in the nose were now removed.

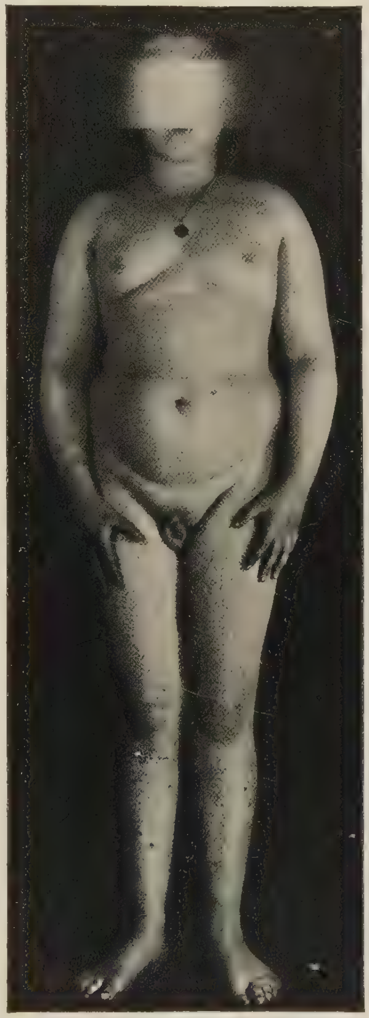

FIG. 68.—Case of eunuchoidism (Observation XLVIII).

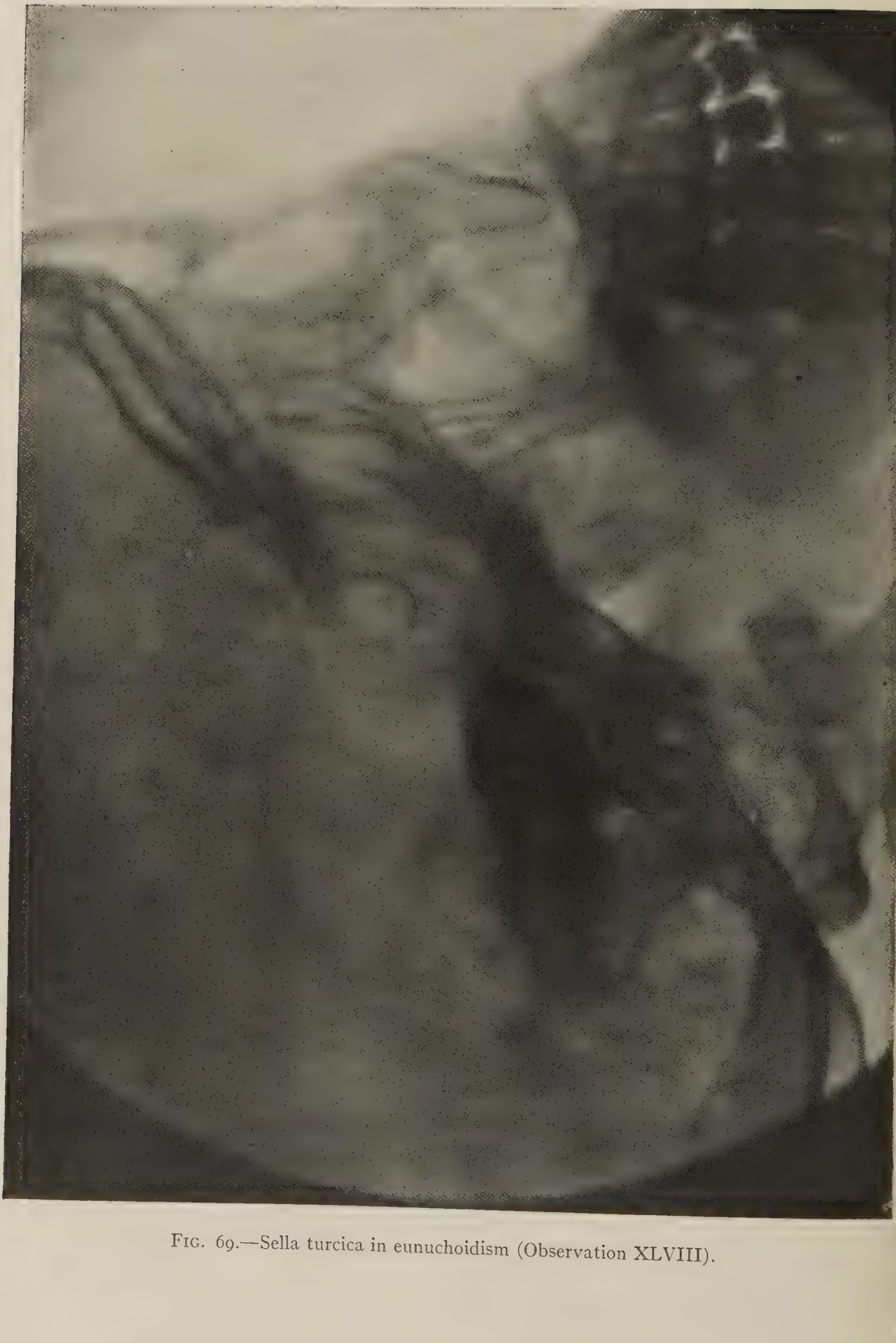

FIG. 69.—Sella turcica in eunuchoidism (Observation XLVIII).

Summary.—Here was a typical case of eunuchoidism. The headaches and the occasional vomitings at first awakened the thought of a hypophysial tumor; but the X-ray examination of the skull and the observations continued for three years, and especially the absence of an inhibition of growth, ruled out this possibility, the inhibition of development seemed to be only transitory, that has recently been made up for very considerably.

*Observation XLIX.*—Dat. from Jerusalem, twenty years old. Entered the clinic Dec., 1905. Typhoid fever at the age of sixteen years; since this time chronic enteritis. Total length 159 cm., circumference of head 57 cm., of breast 74 cm., of abdomen 87 cm., anterior superior spine to internal malleolus 88 cm., acromion to styloid process of radius 57 cm., acromion to oleocraonn 35 cm.

Distantia spin, 26 cm.

Distantia crist, 27½ cm.

Distantia trochant, 29 cm.

Slender build, marked emaciation, except that there are fat deposits on the hips and mons Veneris. Milk-teeth in part retained. The penis and scrotum quite small. Testicles on both sides in the inguinal canal; very few hairs at the root of the penis. No hairs in the axillæ, no beard. Never erections, no libido.

Marked hyperextensibility of the joints, especially the phalangeal joints of the fingers. The fingers can be bent backward to a right angle, and the knees can rest comfortably in the axillæ. *Fingers are very long and slender.*

Sexual life entirely absent.

X-ray examination shows that the distal epiphysial junctures of the ulna and radius, the proximal of the first metacarpal bones and proximal of the phalanges are still open; the bones seem rarefied.

The sella turcica is rather small.

Striking is a short-sized, round and sharply delineated calcification in the anterior part of the sella turcica immediately beneath the clinoid process.

Slight genua valga.

Voice high.

Indistinct prominentia laryngea.

Thyroid not palpable.

Test for alimentary glycosuria (100 and 150 gm. dextrose respectively) negative.

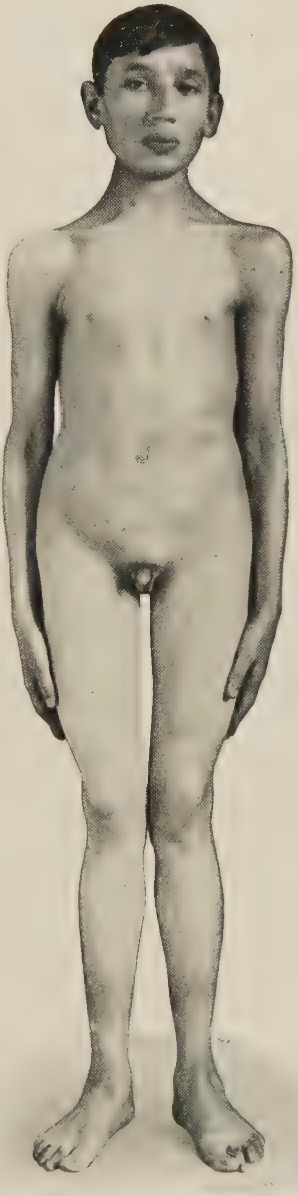

FIG. 70.—Case of eunuchoidism (Observation XLIX).

*Observation L.*—M. W., twenty-three years old. March, 1903. Genitalia hypoplastic, as far back as patient can remember. Deposits of fat on the mons Veneris and hips, which during the last few years have become more strongly developed. Never libido erections often since the eighteenth year, during which the penis becomes about 3 cm. long. Has never had sexual intercourse. Recently several pollutions. Patient is 169 cm. tall.

Length of lower extremities (from ant. sup. spine of ileum to int. malleolus) 87 cm.; length of the upper extremities (from head of humerus to end of third finger) 76 cm. Span width 184 cm., genu valga. Copious deposits of fat on the hips, on the outer sides of the thigh and on mons Veneris. Mammæ not very rich in fat. No beard hairs at all. Abundance of hair on head. Hairs in axillæ sparse; pubic hairs present, not very luxuriant, bounded above by a horizontal line. No hairs on the linea alba. No hairs on the thighs. Genitalia hypoplastic. Penis small, scarcely 1½ cm. long. Each testicle about size of a bean, soft.

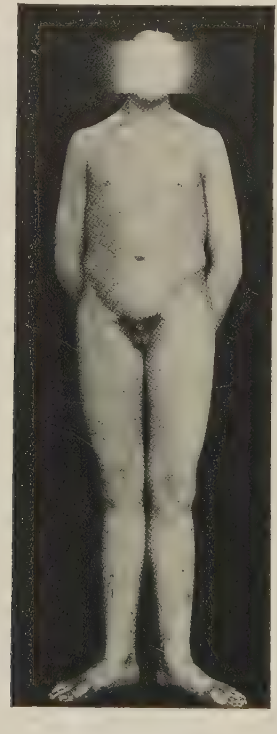

Fig. 71.—Eunuchoidism (Observation L).

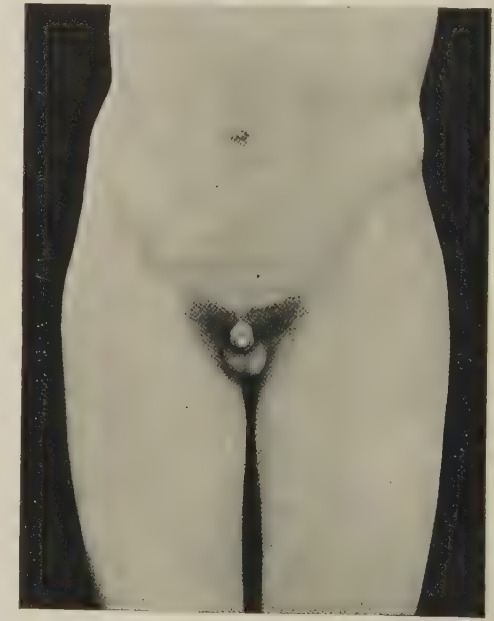

Fig. 72.—Genitalia in case M. W. (Observation L).

X-ray.—Sella turcica normal, the distal epiphysial junctures of the radius and ulna, and the proximal of the first metacarpal phalanges are still open.

Leucocytes, 7600 of which 46 per cent. are neutrophilic polymorphonuclear cells. Voice higher. Prominentia laryngea not palpable. Thyroid gland not distinctly palpable. Test for alimentary glycosuria (100 and 150 gm. dextrose) negative. Character: Silent, not communicative, somewhat shy. Intelligence normal.

*Observation LI.*—H. Ad., twenty-eight years. Entered clinic April, 1912. The patient had nine brothers and sisters, five of whom died shortly after birth. One sister had chlorosis. One brother when a child apparently had laryngospasm. Since his sixteenth year the patient has suffered with a gradually increasing chronic exudative articular rheumatism. He states that once during an exacerbation of the joint affection, he lost much weight. Then in the twenty-first year he was at a bath-resort and in a short time

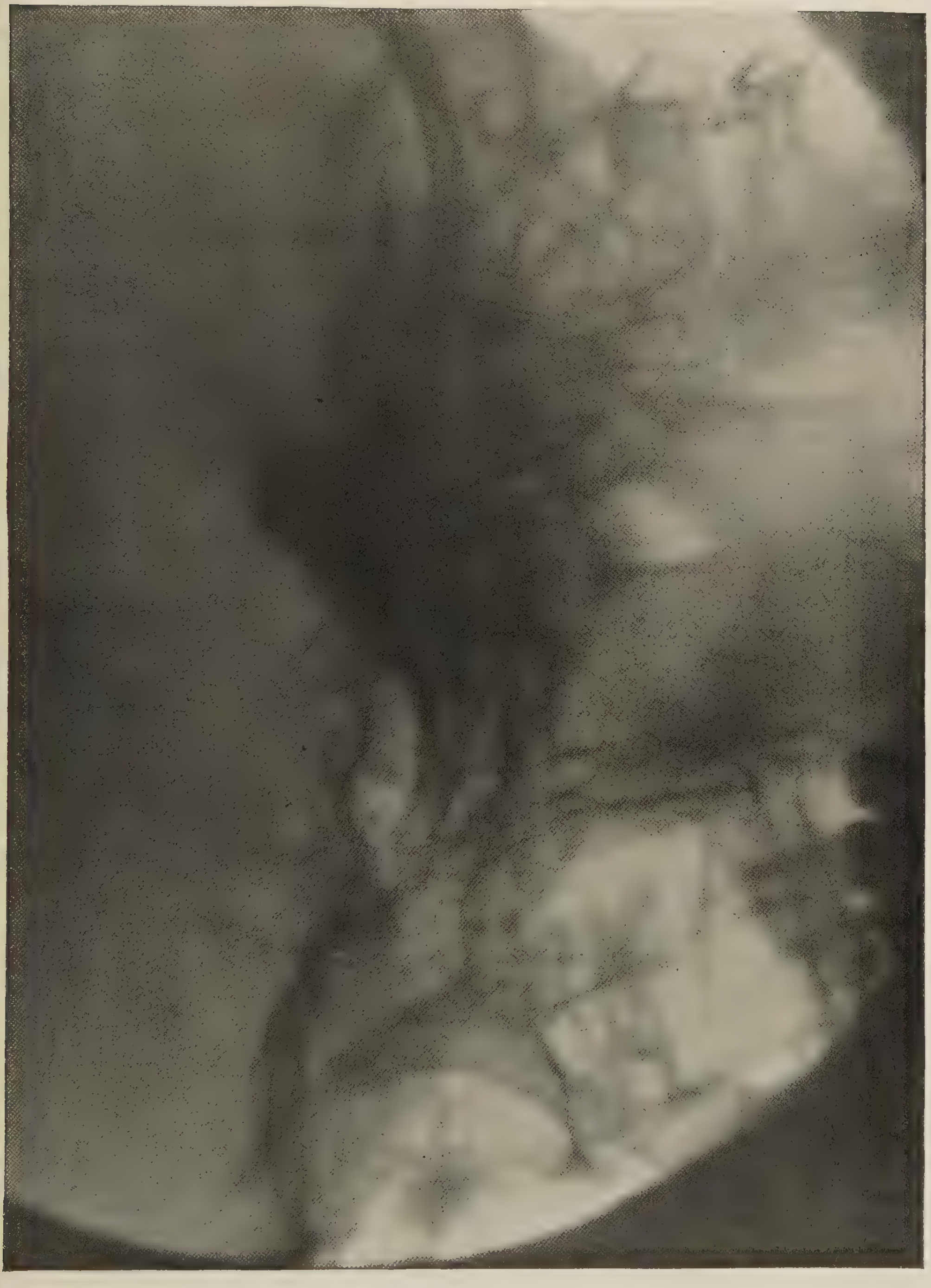

FIG. 73.—Sella in a case of eunuchoidism (Observation L).

gained 42 to 48 kg. Later this became obesity. Then during another attack of articular rheumatism he again lost weight. Now the body weight is 66½ kg.

The patient states that he has experienced sexual sensations since the twelfth year of life. Later he often had erections, in which the penis became quite stiff. His inclination was always for young boys, however, and occasionally he practised active pederasty. Since his sixteenth year, his inclination gradually turned to women, but the libido was never very strong. He had love-episodes but he never attempted coitus, as he knew that he was impotent. Later never pollutions, and the penis has always been very small.

The patient is 176 cm. tall, of typical eunuchoidal form and dimensions. The span-width is 185½ cm., the lower length nearly 100 cm. The thorax is small in relation to the pelvis, the head is small, the prominentia laryngea is only indicated. Bilateral genua valga.

The patient is very intelligent but very taciturn, speaking only when he is spoken to. The [mental] attitude is often depressed.

The voice is high, the thyroid gland not distinctly palpable. Typical distribution of fat, and a thick pad of fat on and superior to the mons Veneris. Marked fat collection in the hypogastric region, which is separated from the mons Veneris by a deep fissure, also fat on the outer sides of the thighs and on the buttocks. The breasts are very rich in fat. On the hips are striæ (the results of former obesity).

*Hair.*—No beard, no axillary hairs, hairs on the mons Veneris only sparse, forming a horizontal line above. No perineal hair. Hair on the trunk otherwise absent.

The penis is 3 cm. long, as in a five-year-old boy. The testicles are palpable in the scrotum, about the size of beans, very soft. The prostate is very small.

The breadth of the heart as shown by X-ray examination is only 10½ cm.

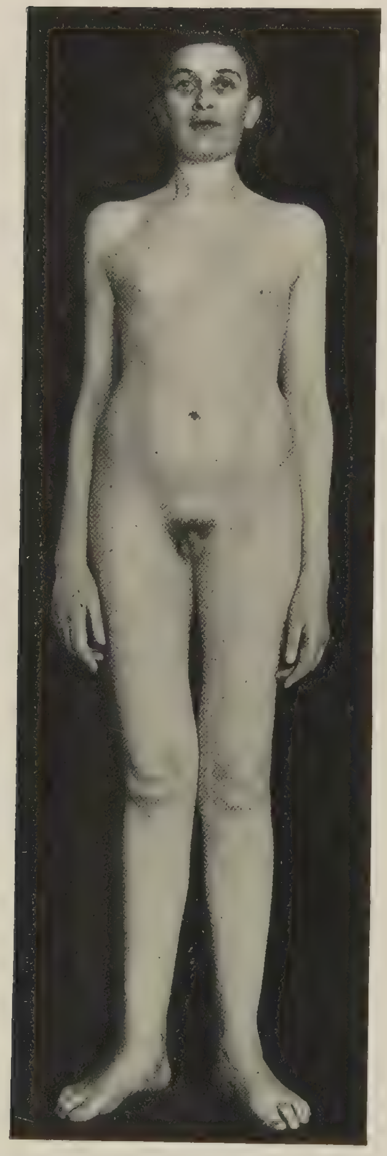

FIG. 74.—Eunuchoidism (Observation LI).

The X-ray examination of the skull shows a small but otherwise well formed sella turcica. It also shows that the promenial epiphysial junctures of the head are still open, the distal are closed. Open are the proximal of 'the first metacarpal and distal of the radius and ulna.

Blood examination: Erythrocytes, 5,800,000.

Hemoglobin, 75 per cent.

Leucocytes, 5500, of which:

Neutrophiles, 59 per cent.

Lymphocytes, 16½ per cent.

Large mononuclears, 21½ per cent.

Eosinophiles, 3 per cent.

Examination of the respiratory metabolism (*Dr. Bernstein*).

| $CO_2$ in cc. | $O_2$ in cc. | |
|---|---|---|
| 176.5 | 221.0 | |
| $CO_2$ | $O_2$ | RQ |
| 2.67 | 3.31 | 0.8088 |

According to this the oxygen consumption is entirely normal.

Test as to alimentary glycosuria (100 and later 200 gm. dextrose negative).

Summary.—Typical case of eunuchoidism, in which a slight function of the sexual glands was present at the time of puberty, which, however, soon disappeared.

**Symptomatology.**—The form of eunuchoids is characterized by its slenderness. Also in fat individuals is the bony build slender, and striking are especially the tubular bones by their length. The head is small, the hands are slender and long. This is well shown in the accompanying photographs. Tallness is the rule in most of the cases. There are cases known that were nearly 200 cm. tall. As far as I can judge by the literature, individuals with eunuchoidism who are not pronouncedly tall are never, on the other hand small. In the case I reported the height is never below what corresponds to the age. Only case Da is small, but here the parents are very small. Hence there usually exists abnormal tallness and at all events never, unless especial complications should exist, stunting of growth. We shall see later that this is important for differential diagnosis from hyopophysial dystrophy.

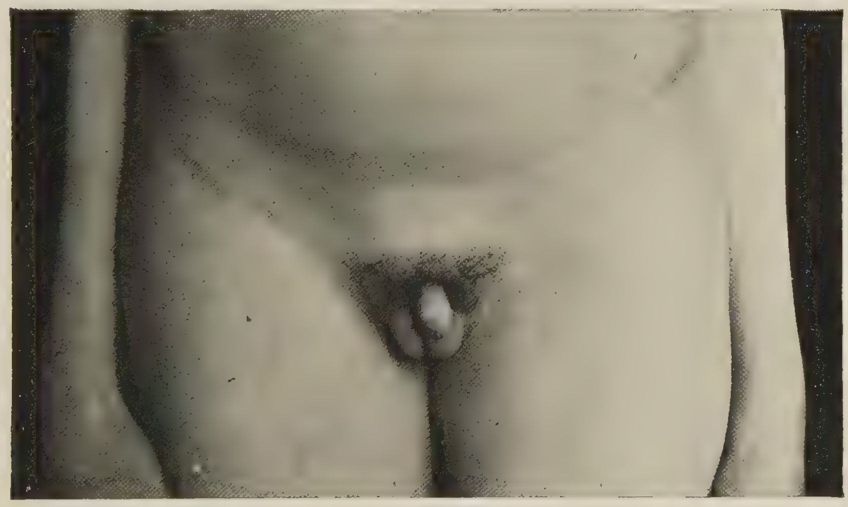

Fig. 75.—Genitalia in Case H (Observation LI).

The dimensions of the skeleton in eunuchoidism are characterized by the especial length of the extremities. There is almost always found an excess of the lower length over the upper length and of the span width over the body length. I quote some examples. In the case of *Duckworth* the body length

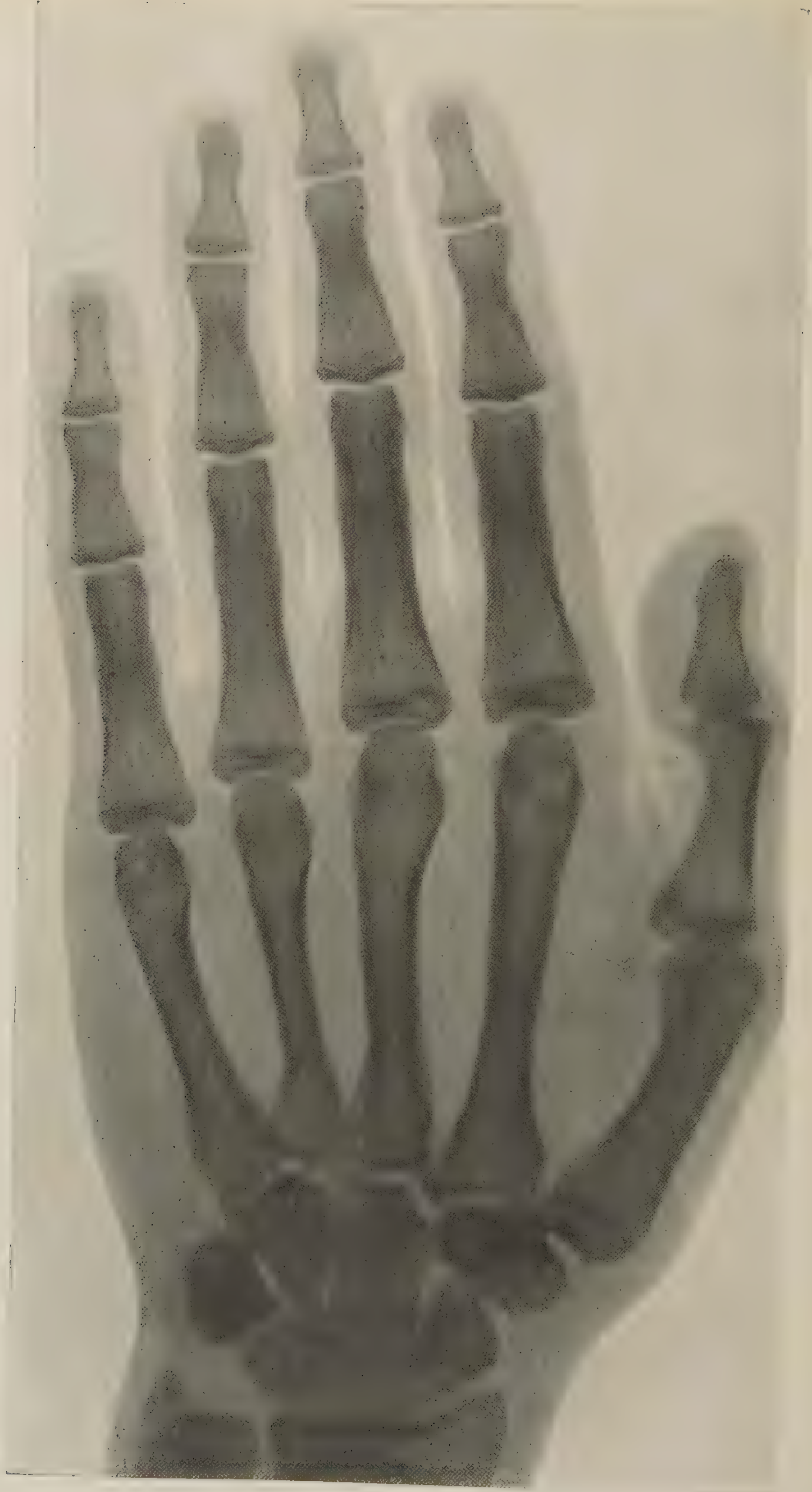

FIG. 76.—X-ray picture of the hand in eunuchoidism (Observation LI).

was 171.7 cm., the span width 179 cm. in Observation LI, H., the length was 176 cm., the span width 185½ cm., the lower length 100 cm. In Observation L, the height was 169, the span width 184. The tallness and the preponderance of the length of the extremities is brought about by an abnormally long remaining open of certain epiphysial junctures, namely, those which usually ossify the latest. According to *Tandler* and *Grosz* they are chiefly the following: The sternal end of the clavicle, the proximal end of the humerus, the distal ends of the radius and ulna, the distal of the tibia and fibula, the crista ilei, the tuber ischii. Often at the site of the coronal and the parietooccipital sutures is found a tertiary suture formation. The root of the nose is often deeply saddled. On the contrary the bone-nuclei are apparently always correspondingly well-developed. At least in Observation Sch, I could find at the fourteenth and at the sixteenth years of his life that there was a development of the bone nuclei corresponding to his age. Also in Observation W. M. (twenty-three years) and in Da (twenty years) the bone nuclei are already developed very well.

At later years the junctures may be fully closed (Case *Thibierger* and *Gastinel*).

The sella turcica, so far as observations have been made on it is normal in size or rather small (*Tandler* and *Grosz*, also the *author's* observations. This agrees with the observations of *Eppinger*, that in women with infantile genitalia, the sella turcica is rather small. In my case a small focus of calcification was found on X-ray examination (Observation Da).

Almost always there are genua valga. These were always present in my cases. Moreover, I could often observe the hyperextensibility of the joints, especially of the phalanges of the fingers (confer case Da). At the diaphyses the bones are commonly rarefied.

The dentition is sometimes retarded. In Observation Da, milk-teeth were present at the twentieth year.

The larynx remains cartilaginous and retains the dimensions of childhood. The angle of the laminæ thyroidæ remains wide. The prominentia laryngea is only slight. In highly pronounced cases voice remains high and is usually shrill.

All cases show the typical distribution of fat, that is, pads of fat on the mons Veneris and the hypogastric region, which latter is separated from the mons Veneris by a deep furrow. Moreover, there are copious fat deposits on the buttocks and on the outer sides of the thighs, and fat deposits in the breasts. *Tandler* and *Grosz* distinguish, as in true eunuchs, a tall and a fat type. The tall individual always shows the eunuchoid distribution of fat, however. Also in these individuals who from some reason or other have lost weight, is the distribution of fat always at least indicated by an inclination to become fat. When the conditions are favorable, the obesity develops suprisingly rapidly (confer Observation H). It may attain an excessive degree. *Tandler* and *Grosz* report a case in which a 6 kg. pad of fat was removed by operation from the hypogastric region, which removal seemed to make the patient easier.

The hair of the head is abundant. There are often lanugo hairs on the face, especially in front of the ears and on the chin and upper lip. There are no mustache and beard. In later years occur on the lower jaw sparse bristly hairs, such as are seen in old women. The hair in the axillæ is absent or only sparse, that on the mons Veneris is limited to a few short hairs at the root of the penis. When they are more abundant in this situation they are limited above by a horizontal line. There are no hairs on the perineum; nor on the trunk and extremities.

The skin is remarkably delicate, pale, velvety, and sometimes has a fawn-yellowish color. The face in older individuals often shows folds and wrinkles.

As a rule the musculature is but little developed, and shows but slight tonus.

In most cases the thyroid glands seem to have a slighter volume, at least the statement is repeatedly made that the thyroid was not palpable.

The genitalia are pronouncedly hypoplastic. The penis is always very small and sometimes quite buried in the fat pad on the mons Veneris. The scrotum is small and smooth and hairless. The prostate is small. The testicles are small, soft and sometimes not larger than a pea. Sometimes they are not or only partially descended on one or both sides. In this case the inguinal canals are open. Autopsies were made in the case of *Etienne, Jeandelize* and *Richon*, and in the case of *Duckworth* and of *Tandler* and *Grosz*. In the case first named the testicles were very small, fibrous (3 gm.), the interstitial glands were degenerated. Also the prostate was very fibrous. On microscopical examination, *Tandler* and *Grosz* found sparse seminal canals and sparsely developed interstitial substance. Also the seminal vesicles were small, but the epididymis on the other hand, well developed.

Cases of female eunuchoidism seem to be rare. *Josefson* and *Lundquist* have reported such a case, which I shall quote somewhat in detail.

> Thirty-four-year-old woman who had kept on growing from the fifteenth year on (the growth had been especially active up to the twenty-fourth year); she was 183.6 cm. tall (upper length 118 cm.), she had never menstruated and had felt only slight inclination for men; the mammæ were small, flat, without palpable glandular substances, the nipples very small; she had rather a mannish appearance, but a feminine voice. The form of the pelvis was rather womanly. The epiphysial junctures were closed, the sella turcica not enlarged. Examination of the genitalia showed very small labia minora, a hypertrophic clitoris, the vestibule was rather narrow, the internal genitalia were not palpable. No introitus vaginæ or hymen.

In eunuchoids the genital function is always markedly reduced or entirely absent. In many cases, however, erections are possible despite the smallness of the penis. I refer to the Observations Da and H. In many cases libido is entirely absent, although it may be present slightly. In one of my cases the inclination was at first contrasexual. In many cases potency can exist for some time, but this becomes less after some years and disappears. In other cases the inhibition of development and disturbance of function occurs chiefly at the time of puberty and later becomes compensated (transitory eunuchoidism). We may regard both as formes frustes. As a case of the first form I would regard case II of *Josefson* and *Lundquist*. It was that of a forty-five-year-old man who had been married since the thirty-sixth year and who was entirely impotent for three years. The breasts had been very rich in fat ever since youth and the pubic hairs ended above in a horizontal line, the voice had not changed, the hairs of the beard and in the axillæ were very sparse, trunk hairless.

Eunuchoids of the male and female sex are always sterile. At least no case of procreation or conception is known.

In woman, the breasts are poorly developed or fatty, but poor in glandular substances; in man they often contain much fat.

Observations on the respiratory metabolism have as yet been confined to Observation H and to a female eunuchoid of *L. Zuntz's*. The value of $O_2$ requirements is entirely normal. Of course from which we are not justified in concluding that in such cases we may not have had a slight degree of endogenous obesity, as small differences may not be evident on investigation, and yet through summation may favor deposition of fat. It is certain that in all these cases there is present an abnormal disposition for the deposition of fat, as was observed for example in the case of H. At all events the cause may be due chiefly to the slight inclination for movement and to the individual's phlegma.

Test for alimentary glycosuria was undertaken in three of my cases, with 150–200 gm. dextrose, and always resulted negative. Hence the assimilation limits for carbohydrates seem to be high.

*Guggenheimer* reports a case in which at an old age diabetes developed. I cannot see here an especial connection with eunuchoidism. In eunuchoidism (as in normal individuals) there may very well set in a degeneration of the pancreatic insular apparatus. Another case of eunuchoidism with diabetes seems to be the "giant" described by *Uhthoff*. This patient at the age of sixteen years suffered an attack of pneumonia. From then on abnormal growth. He was 194 cm. tall, hands and feet were not especially large. There existed bilateral cryptorchidism, the pubic hairs were sparse, and he had never been potent.

The purin metabolism has been studied (not published) in one case only, Observation H by *Nowaczinski* and *myself*. The endogenous uric acid elimination was normal. Purin administered exogenously was well eliminated. Perhaps this behavior is of differential diagnostic importance as against hypophysial dystrophy.

The blood examined in my case showed normal values for erythrocytes and hemoglobin. The leucocyte count was near normal; in all cases there existed a pronounced mononucleosis. Lately also *Guggenheimer* has found the marked predominance of lymphocytes in several cases of eunuchoidism; in one case he saw hyperleucocytosis with predominance of the mononuclear cells.[1]

The thymus gland showed abnormally slight involution (*Kolisko*, and *Tandler* and *Grosz*).

The findings in the internal organs show no essential alterations, except such as must be regarded as coincident. In one case the heart shadow as shown by the X-ray was seen by me to be strikingly small.

Perhaps the excitability of the vegetative nerves is in cases of eunuchoidism somewhat reduced. This was tested in some cases with pilocarpine and adrenalin, yielding a slight, but distinct reaction.

The development of the intelligence in such individuals is mostly entirely normal. Feeble-mindedness, which has been observed in some cases, is to be referred to other coincident developmental disturbances. On the contrary, certain common traits do exist in the psyche of eunuchoids. They are, as *Tandler* and *Grosz* notice, strikingly quiet, but little communicative, and often but slightly independent. At any rate this mental condition is not to be designated as infantile. The masculine quality is all that is lacking.

**Occurrence and Pathogenesis.**—Eunuchoidism, at least as far as its pronounced forms are concerned, occurs essentially more frequently in the male sex. Thus far the only typical incontestable case in woman has been reported by *Josefson* and *Lundquist*. Perhaps to this may be added the previously quoted cases of *Swinarski*, *Pfannenstiel*, and of *Howitz*. But here there are no statements as to the proportions of the body, which would be very important for the diagnosis. Animal experiments show us that castration in early life produces long-legged individuals in the female also. We know very little as to the cause of the developmental disturbances in the sexual glands. As was mentioned previously, eunuchoidism in the male sex is very frequently associated with cryptorchidism. This may be either abdominal or inguinal. It may well be regarded as a partial manifestation of the developmental disturbances and not as its cause. Moreover the developmental disturbance may very well be congenital if it first manifests itself at the age of puberty.

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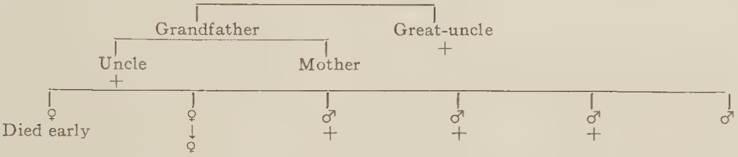
[1] *Guggenheimer* states that in two cases of eunuchoidism he found hyperglobulia. He mentions, moreover, that in these cases after the injection of adrenalin there never occurred an increase of erythrocytes, but even diminution of these. He says that he could not "corroborate" the hyperglobulia after injection of adrenalin as observed by *Bertelli*, *Schweiger*, and *myself*. This expression seems to me out of place. We have never asserted that we saw hyperglobulia after the injection of the doses of adrenalin used in man. The hyperglobulia observed by us in the dog after larger doses had already declined after twenty-four hours. *Guggenheimer*, however, tested very small doses of adrenalin twenty-four hours after injection. The individual values for the erythrocytes in *Guggenheimer's* case also varied appreciably in the days uninfluenced by adrenalin.

It is also conceivable that traumatic and infectious insults in early youth may damage the sexual glands and thus lead to eunuchoidism. This is especially true of mumps, perhaps also of scarlet fever, measles, etc. We shall meet with these etiological factors again in the consideration of late eunuchoidism. Not rarely is eunuchoidism hereditary. The case concerned in direct reproduction can be only the lightest case, those principally associated with obesity in childhood. On the contrary, it is conceivable that in a family cases may now and then crop up, that do not propagate. Such a familial occurrence has been reported by *Sainton*. Of five living brothers and sisters, three were eunuchoids and besides this an uncle and great uncle.



Very noteworthy is the observation that eunuchoidism and chlorosis can occur in the same family (*Tandler* and *v. Noorden*) (see also Observation H).

**Differential Diagnosis.**—Differential diagnostically, chiefly infantilism and hypophysial dystrophy come into consideration. The former in the pure forms shows retention of the childish dimensions. Also the psyche remains infantile; but the psyche of male eunuchoids although mannish, can hardly be called childish. *Peretz* and *Wolf* are wrong in their attitude against the delimination of the eunuchoid type. When they call eunuchoidism a pure form of infantilism, they are confused as to the meaning of the diseases. Both the female individuals that *Peretz* describes are to my mind not eunuchoids, but infantiles (see Chapter XII, Infantilism). Naturally there occur also mixed forms of infantilism and eunuchoidism, hence cases of infantilism in which the development of the sexual glands not only remain at a childish stage, but their function is much more seriously disturbed. It must not be forgotten that normally the interstitial glands functionate also in children, even if a subordinate degree only. Such cases show in addition to the infantile features also more or less distinct eunuchoid dimensions and the typical distribution of fat such as is not a feature of true infantilism. The four female cases of *Wolk* are also not true eunuchoids. One of them is apparantly a true dwarf, the others are cases of infantilism, or at least transitional cases which tend nevertheless more toward infantilism.

The differentiation from hypophysial dystrophy is mostly not difficult. Common to both are the genital disturbance and the association of fat distribution or obesity. Hence there are an eunuchoid and hypophysial form of dystrophia adiposo-genitalis. The two forms are different from each other:

1. By the growth in height. In the hypophysial form, so far as it sets in

in childhood, is found pronounced inhibition of growth; in the eunuchoidal form is found even tallness, or at least no growth disturbances.

2. Eventually through the behavior in metabolism. In the severe forms of hypophysial dystrophy the fundamental exchange is usually distinctly reduced in the end; in the eunuchoid form the reduction is perhaps not considerable enough to become demonstrable. The answer to these questions will depend on further investigations.
3. Through the cerebral manifestations in hypophysial dystrophy. Here in most cases are found signs of a hypophysial tumor or of, at least, a tumor in the hypophysial region, or at least signs of increased brain pressure. One should not forget, however, that cases of eunuchoidism at the time of puberty not at all rarely complain of headaches; and occasional vomiting may occur (two cases under my observation). In such cases the X-ray examination of the sella is very important. At all events there are also processes that may destroy the hypophysis without distinctly altering the sella and producing symptoms of brain-pressure; for examples gummata or chronic inflammations. Such processes indeed set in after completed development. Hence here comes into consideration the differentiation from late eunuchoidism or from multiple ductless glandular sclerosis.

The blood examination in the hypophysial as well as the eunuchoid form mostly shows a pronounced mononucleosis. Hence here there is no distinguishing factor. We can at most say that in the hypophysial form, at least in the severe cases, the hemoglobin and the erythrocyte count are often more markedly reduced.

**Prognosis and Treatment.**—Very important is the observation of *Tandler* and *Grosz*, that in the eunuchoidism that sets in early, developmental disturbances of the sexual glands are often only temporary (prepubertial eunuchoidism). Hence such cases may be improved. One of my cases showed such a condition. At the sixteenth year (Observation Sch) the voice had changed, the genitalia had developed almost normally, but as yet there had occurred no pollutions. Also the obesity is only improved for the abnormal distribution of fat still exists. In such cases we would recognize the developmental disturbances later in life by the distribution of fat, and probably also by the hair condition. Also it is very probable that in these cases the function of the sexual glands disappears prematurely. Case II of *Josefson* and *Lundquist* seems to point in this direction.

Rapid improvements have been reported from the thyroidin treatment. *Apert* mentions a case complicated with cryptorchidism in which after one-half year's treatment with thyroidin, the penis had distinctly grown, the testicles had lowered, and the weight had increased about 2½ kg.

Also *Parhon* and *Mihailesko* report a similar case in a fourteen-year-old youth with left-sided inguinal cryptorchidism and obesity; under thyroidin treatment the genitals took on a rapid development.

There is no doubt that we are often able to improve with thyroidin the fat types of obesity. Thus for example in Observation Sch, there occurred without limitation of diet, after the administration of even small doses of thyroidin, a rapid reduction of 3 kg. in weight. A considerable improvement is also reported by *Lemos Magelhaes*. In a case of adipositas nimia who weighed 160 kg. there occurred under thyroidin treatment a reduction of 32½ kg. Then intoxication symptoms appeared. I do not feel justified, however, in referring offhand, as do *Apert*, *Parhon* and *Mihailesko*, the improvement in the genital sphere to the thyroidin treatment, or in constructing, because of the improvement, an etiological connection. To me the reports do not seem convincing that these cases were cured by thyroidin, because as has just been mentioned, there have been sometimes observed in this growth period improvements that are spontaneous. But we must accept a certain stimulating action of thyroidin.

Not much has been reported as to other methods of treatment. I do not know that extracts of sexual glands have been used. As radium emanations have a certain stimulating action on the sexual glands—*Freund* and *I* saw several times through radium treatment an increase of the potency, a recurrence of the periods at the climacteric or an aggravation of dysmenorrheic complaints—in one case (Observation Sch) I used the radium emanation, perhaps with good results. Such a result is to be expected only in youthful cases. In another case (Observation H, twenty-eight years old), who on account of his joint affection was treated for a long time, all action on the sexual glands remained absent.

The transplantation of the sexual glands has not to my knowledge been tried in the treatment.

## 4. Late Eunuchoidism

**Historical.**—The first excellent description of this disease we find in *Larrey* in his "Campagne d'Egypte: de l'atrophie des testicules." *Larrey* observed in several soldiers who had followed the campaign in Egypt with Napoleon and later, in soldiers of the Imperial Guard, simultaneously with gradually occurring atrophy of the testicles with retrogression of the penis, disappearance of the libido and the potency, falling out of the pubic and axillary hairs, development of a falsetto voice, and certain alterations of intelligence and psyche. *Larrey* sees the cause of the disease in the deleterious influences of the climate, or in sexual abuse or in alcoholism. Lately interest has again been turned toward this subject by *Gandy* who described three cases, that he termed infantilism reversif ou tardif. Of *Gandy's* cases I would regard two as typical cases of late eunuchoidism. The third belongs to multiple ductless glandular sclerosis. *Gandy* seeks the cause of the affection chiefly in a dysthyroidism, while *Claude* and *Gougerot* describe a series of cases that they refer to an insuffisance pluriglandulaire endocrinienne. *Cordier* and *Rebattu* treat the subject in a large study of these cases; they again uphold the designation "infantilisme regressif type *Gandy*."

Recently I have published a study on this subject in which I pointed out that the manifestations in this disease, so far as they connected with the genitals, are like those of eunuchoidism; and I selected from the group the pure cases of "late eunuchoidism" ["Späteunuchoidismus"] from late eunuchoidism which is only the partial manifestation of a very complex clinical picture.

**Definition.**—*I term "late eunuchoidism" a clinical picture that comes about by the fact that in an already matured organism in which also the functions of the sexual glands have attained their full development, there occurs atrophy of the accessory genital apparatus (in man retrogression of the penis, scrotum, the prostate, etc.; in woman the labia majora and the uterus), and retrogression of the secondary sexual characters (mustache, beard, hairiness of the axillæ and the pubis, the trunk and the extremities).* Moreover there *develop more or less distinct collections of fat on the breasts, the mons Veneris, and the hips, and often certain alterations of the psyche.* The typical eunuchoidal alterations of the skeleton can no longer go on developing, especially where the development of the skeleton has been already closed off; that is where the epiphysial junctures have already united.

*There is regularly found a high-grade affection of the sexual glands, that must be regarded as the cause of the manifestations described.*

**Case Reports.**—I have already treated in my publication the case histories of this affection somewhat in detail. Since the time I wrote my article I have found still more cases in the older and newer literature. As I would describe the clinical picture in detail and delimit it as precisely as possible, I will here make a complete report of the case histories. Then I shall classify the cases according to their etiology, as nearly as possible. Moreover, I would here state that the position of a series of cases is still uncertain. I shall come back to these cases in the consideration of multiple ductless glandular sclerosis, and here set forth only those cases which I regard as pure cases of late eunuchoidism or at least as cases in which the manifestations of late eunuchoidism stand quite in the foreground.

A. Cases that depend on a *traumatic foundation.*

*Observation of Achard and Demanche.*—Sixty-eight-year-old man. Pale tinge, the skin of the entire body pale and dry. Hair of head abundant, skin of the face and trunk and extremities completely bald. Eyebrows sparse. The breasts not essentially enlarged. The scrotum small, both the testicles small, the cremasteric reflexes very weak. Intelligence normal. Easily excitable disposition; at the twenty-fifth year of life, the man had sustained an injury, due to the tread of a foot, in the scrotal region. The testicles had become swollen, as the result of the injury, and later atrophied. Beard and cranial hair, that previously had been abundant, became at the same time always sparser, the muscular strength decreased, a certain amount of libido was retained, but ejaculations had never occurred.

*Observations of Gallavardin* and *Rebattu.*—Twenty-six-year-old man, 174 cm. tall, looks like a fifteen-year-old youth. Preponderance of the lower length over the upper length (femur + tibia = 90½ cm.). The distal epiphyses of the radius and ulna have as yet not united. The voice that previously had been mannish, is now shrill, the skin is white and delicate, scrotum and penis are very small (as in a six- to ten-year-old boy).

At eighteen and one-half years of age the man had received a violent knock in the scrotal region, after which for three hours he was unconscious. After this there developed a considerable swelling of the testicles and bloody suffusion of the skin of the scrotum; these phenomena disappeared after three months. Later the testicles became small, the penis atrophied, the secondary sexual characters and the libido disappeared, and complete impotence appeared. The photograph accompanying the report of the case shows well the eunuchoidal fat distribution.

*Observation of Cordier.*—Twenty-nine-year-old man, looks like an eighteen-year-old youth. Genitalia and prostate markedly atrophic, secondary sexual characters and libido have almost disappeared. The man married at the age of twenty-five years, is the father of one child. At twenty-five and one-half years a trauma that affected the testicles. Gradual falling out of the hairs of the mustache, the beard since then has become very sparse, marked reduction of libido.

*Observation of Stieda.*—Thirty-year-old man. At the age of fifteen both testicles bruised. From then on the testicles became gradually smaller, he first remained behind in growth and then grew appreciably between the twentieth and thirtieth years. The voice was only somewhat rough, and the potentio coeundi remained, although there was no ejaculation of semen. The mammary glands grew somewhat in circumference. According to his statement a growth about the size of a thaler appeared at their site on each side. The man remained beardless, there was hair on the mons Veneris but the upper border of this hair was horizontal. Height 175 cm., the extremities were remarkably long, the breadth of the shoulders was slight, the pelvis broad, the larynx small, internal and external genitalia had remained behind in development. The testicles were about the size of beans, the epididymises were about just as large.

*Observation of Riedinger.*—The patient in his twenty-first year suffered a severe injury in which the anterior perineal region was bruised and the scrotum torn, and the testicles and prostate severely injured. The penis had previously been of normal size (examined by *Rieder*). Erections were still possible the first year after the injury, but there were no signs of ejaculations. Now erections only very seldom, no sexual intercourse any more. The man is 163 cm. tall, the lower extremities (from the trochanters down) are 86 cm. long, the skin is pale in color, the skin of the face lax and wrinkled. He appears much older than he is. The skin is otherwise lax and flabby. He is very thin; the accompanying photograph allows one readily to recognize, however, the abundance of fat in the breasts and on the mons Veneris. The penis is 6 cm. long, reduced in all its dimensions. The pubic hairs are very sparse and the upper border of the pubic hairiness is horizontal. The hairs in the axillary and anal region are also sparse. No beard (before the injury there was a beard). The voice is mannish, lately a goiter has developed. The sella turcica, as the author kindly informed me in a written communication, is not enlarged.

*Own Observation LII.*—Forty-two-year-old man, rather corpulent, breasts very rich in fat, mons Veneris and hips somewhat more rich in fat. Sparse hairiness of the axillæ. Genitalia rather well covered with hairs. Both the testicles as large as peas, very soft, the scrotum small, without tension, cremasteric reflexes absent. Bilateral scars in the inguinal regions the result of operation.

Four years ago, after operation for bilateral inguinal hernia there developed on each side an enormous hematoma, that after some time disappeared. Only a few weeks afterward the patient noticed diminution of potency, that later diappeared entirely for a time. The libido did not disappear entirely, later erections were again possible and coitus was performed a number of times per month. According to statement, only a slight ejaculation occurred.

The cause of the atrophy of the testicles in these cases may very well be regarded as a circulatory disturbance, whether through injury of the arteries, or compression due to shrinking of scar tissue, whereby damage was done to the nutrition of the testicles.

### B. Cases that depend on an *orchitis* due to *syphilis, gonorrhea*, or *mumps*.

Perhaps some of the cases described by *Larrey* belong to this group.

*Observation of Coffin.*—Male individual, after bilateral luetic orchitis the testicles shrank to the size of beans. The voice became higher, obesity developed, the beard fell out, the muscular power diminished, erections and ejaculations ceased, the penis became smaller, finally to the size of that of a six- or seven-year-old child. The breasts became larger.

*Observation of Charcot.*—Soldier. After bilateral mumps, orchitis, atrophy of the testicles to the size of beans. Libido disappeared, complete impotence, the breasts increased in size.

*Observation of Lereboullet.*—Twenty-seven-year-old man, skin pale, eunuchoid form, breasts well developed, penis and testicles very small, impotence. Beard absent, the patient was formerly very potent and the beard well developed. The voice mannish. At twenty-four years, mumps with bilateral orchitis, later gradual atrophy of the testicles.

*Observation of Dalché.*—Thirty-six-year-old man. Color of face pale, hair of beard abundant. Hairs of beard, axillæ and genitalia, are entirely absent. Testicles very atrophic, libido absent, complete impotence, intelligence weak, forgetfulness, tendency to weep, apathy; often chills. At twenty years lues, at thirty years, bilateral orchitis, since that time development of the genital atrophy. Later also slight swelling of the legs and the face. Polyuria. In this case the eunuchoidism is certainly in the foreground. But in addition there exist symptoms (and indeed chiefly symptoms of failure) on the part of the other ductless glands.

*Observation of Dupré.*—Forty-five-year-old man. Abundance of hair on head. Mustache much reduced, very little pubic hair, pallor of the face; penis and testicles small, soft, libido absent, impotence. Formerly gonorrhea and syphilis. At the thirtieth year gradual testicular atrophy and development of the symptoms described.

*Observation of Gandy.*—Forty-six-year-old man. Color of face pale-yellowish, secondary sexual characters very sparingly developed. Genitals markedly atrophic, some collection of fat on the trunk. Impotence. Formerly entirely normal, lues at the thirty-third year. About this time beginning of the retrogression of the genitalia, and secondary sexual characters, temporary polyuria (in the thirty-sixth year), also temporary swelling of the face.

*Observation of Gandy.*—Forty-two-year-old man. Face very pale, wax-like, skin of the forehead arranged in fine parallel folds, skin of the trunk delicate, voice monotonous, no hair at all on lips or trunk, penis and testicles very small, prepuce long and folded, cremasteric reflexes absent, no libido; impotence, memory somewhat weakened, apathy, blood-pressure reduced. At thirty-two years of age bilateral gonorrheal orchitis; from about this time began atrophy of the genitalia and impotence. At the twenty-ninth year states that he is somewhat stronger; pad-like swelling of the skin of the face, the hands and the back of the feet.

*Gandy* regards this case as "dysthyreoidie + dysorchidie." I believe, however, that late eunuchoidism nevertheless stands in the foreground.

Apparently also the observation of *Foges* belongs here. After bilateral luetic orchitis there developed a "gynäkomastie." The mammary glands were removed, microscopical examination showing only fat and no glandular substances. Sexual sensation was much reduced.

### C. Cases *of other etiology*.

*Observation of Cordier and Francillon.*—Thirty-five-year-old man. 175½ cm. tall, lower length 90½ cm. hence distinctly predominating. Epiphyses united, eunuchoid distribution of fat, skin pale, diffuse pigmentations. Hairs representing beard absent, hair on cheeks sparse, atrophy of the genitals, libido present but coitus rare and incomplete. Weakness of memory. Patient is quarrelsome, easily excited, slight anemia with hyperleucocytosis and mononucleosis (phthisis pulmonalis is present however). Typhoid fever at about twenty-four years of age. Before development was entirely normal and potency was normal. Several months after the typhoid gradual development of genital atrophy and impotence, temporarily, also, complete loss of libido. Great bodily weakness, that later improved. Since that time increase in height about 3 cm.

*Observation of Gougerot and Gy.*—Fifty-two-year-old man, quite normal up to forty-eighth year (except that he had had gonorrhea); about this time a hard to define acute infectious disease, after this asthenia, polydipsia, polyuria, atrophy of the genitalia, impotence, loss of libido, retrogression of the secondary sexual characters, pigmentations on the forehead, hands and feet, cachexia.

*Observation of Galliard.*—Fifty-seven-year-old man, face very pale, mustache and beard very sparse, no hair in the axillæ, scrotum and penis small, testicles very small, impotence. At fifty-three years eczema, "since that time development of the phenomena described."

*Observation of Belfield.*—In a man twenty-seven years old there developed at the same time with a polyuria a "retrograde puberty," atrophy of the testicles and the external genitalia, retrogression of the secondary sexual characters, etc. The hair of the head remained abundant. Examination took place when the man was thirty-nine years old. X-ray showed sella turcica normal. Thyroidin therapy and later adrenalin were used without results. Later was administered dried suprarenal gland, containing both cortex and medulla. After four months the daily amount of urine had been reduced to one-half. The body hairs had grown distinctly, the testicles were twice as large, and coitus already had been several times performed.

I would here refer to the observation of *Josefson* and *Lundquist* (case 2). We can regard this case as a transition between eunuchoidism and late eunuchoidism. I have described this case in detail in a previous section.

Finally, more on account of the curiosity, I will report an observation described by *Hammond*. The Pueblo Indians in New Mexico seem to have cultivated the so-called mujaderes for purposes of pederasty. For this purpose already fully developed men are excessively masturbated and at the same time are made to ride enormously. This treatment causes an atrophy of the testicles and epididymises, the penis becomes smaller, libido disappears, the testicles are insensitive to pressure, the mammæ enlarge, the individuals become fat, the voice becomes higher and the bodily strength decreases. *Hammond* himself has examined two such individuals. While in many respects the story sounds fabulous (one of the mujaderes stated that he had suckled children), the agreement with the picture of late eunuchoidism is so complete that I had at least to mention the observation.

**Symptomatology.**—Late eunuchoidism is found almost exclusively in men. There have been individual cases reported in women but these are not pure cases. As we shall see later they belong to the group of multiple ductless glandular sclerosis. The cause of the disease in man is either violent trauma effecting the testicles or their vicinity, or, as in my case, probably, a damage to both spermatic cords through shrinking of scar tissue; or a bilateral high-grade orchitis on a syphilitic or gonorrheal basis, or mumps orchitis, or it may be due to severe infectious disease—typhoid for example—or to an infectious process of an unknown nature, affecting the entire organism and probably also the testicles. At the close of these deleterious influences, or also in certain cases quite spontaneously, without distinct recognizable cause, in individuals who previously had been entirely normally developed, in whom especially the secondary sexual characters were completely developed and in whom the genital function has been entirely normal—there develops quite gradually an atrophy of the entire genital apparatus and at the same time a retrogression of the secondary sexual characters.

Finally there seem to be cases in which there exists from youth on a certain lessened valuation of the rudiments of the sexual glands and soon an exhaustion (case of *Josefson* and *Lundquist*).

The ages of the affected individuals are very different. In the case detailed the beginning of the disease fell between the eighteenth and fifty-third years of life.

The alterations in the genitals must be regarded as manifestations of retrogression and not, as *Claude* and *Gougerot* believe, as mere atrophy. In this view I am entirely in accord with *Gandy*. The retrogression of the testicles may be astounding. The testicles are estimated as at the size of hazelnuts, cherries, beans and peas. The diminution of volume is naturally less where connective tissue has formed at the site of an infectious process; and here too there is not such a diminution in consistence; in most cases has been emphasized an especial softness. The scrotum can be as small as that of an eight- to ten-year-old boy; and it loses its tension and its pigments. Also the penis can reduce in size to such an extent that it looks like that of an eight- to ten-year-old boy. The picture is therefore entirely similar to that of early eunuchoidism. Also the prostate takes part in the atrophy.

We have already described the manifestations that occur after castration in the matured woman. Retrogression of the genitalia occurs, mostly an increased fat-deposit and loss of pigment, but not a falling out of the pubic and axillary hair. We shall consider later under ductless glandular sclerosis those cases in which retrogression in the hairiness occurs simultaneously with spontaneous atrophy of the ovaries.

In late eunuchoidism the function of the genitals suffers severe damage. In man complete impotence with entire incapability of cohabitation can occur under circumstances. Libido is here entirely lost; but in other cases only impotence occurs, while libido remains in enfeebled form. In the formes frustes the capability for cohabitation still remains; except that in these cases, as *Cordier* and *Rebattu* point out, much stronger stimuli are needed to induce erection. The cremasteric reflexes are either weaker or entirely wanting. Hence the functional disturbance also corresponds entirely with that of early eunuchoidism.

The same is true for the coloration of the face. The pallor of the face and the delicacy of the skin and body are noted in all cases. There is often found a yellowish tinge; and (in one case) folding of the skin of the forehead (as in eunuchs). Puffiness of the skin of the face is very rare indeed among the cases reported.

The hair of the head remains abundant, but as a rule is rather dry. (The cases with patches of alopecia do not belong to pure late eunuchoidism.)

In severe cases the hair of the body falls out entirely. The mustache, that previously may have been very luxuriant, falls out entirely or at least thins out very much. The same is true of the beard; often is found the statement that the patients who previously had to shave several times a week, shave much less frequently. Thinning out of the lashes and the eyebrows does not indeed belong to the pure picture of this disease. Also the trunk and the extremities may become entirely bald. The axillary hairs, the hairs on the scrotum, the perineum, and on the root of the penis, may fall out altogether.

Very important for the comprehension of the disease picture are the alterations of the form. As has previously been mentioned, it is in itself suggestive that where the beginning of the disease falls at an age where the total epiphysial junctures are closed, a development of the eunuchoidal skeletal type is no longer possible. Of especial importance, therefore, are the observations of *Gallavardin* and *Rebattu*, of *Cordin* and *Francillon*, and of *Stieda*. In the first case a youth of eighteen and one-half years old suffered a knock in the scrotal region, and in the second the beginning of the disease lay in the twentieth year. In the first case there was only a suggestion of the eunuchoidal-skeletal type (predominance of the lower length over the upper length), and the epiphysial junctions that close at a later period were still open at the twenty-sixth year. In the second case there was a further growth of about 3 cm. at the twenty-fourth year. The case of *Stieda's* sustained a trauma in the fifteenth year of life. He first remained behind in growth and then grew appreciably between the twentieth and the thirtieth years. Here, therefore, the epiphysial junctions had remained open abnormally long. Here also there came about the development of the eunuchoidal dimensions.

The influence on the weak parts is noted more frequently. In many cases the statement is made that there appeared at the beginning of the disease an adiposity; in other cases that the breasts had become fatty, or the hips rounded, or that the mons Veneris had become richer in fat. In several cases, in which the typical distribution had not been noted especially, it could be recognized in the illustrations that accompany the reports.

In the majority of cases it is furthermore stated that the voice which had previously been mannish, altered in the course of the disease. It did not come to the development of a falsetto voice, as in eunuchs and early eunuchoids, but the voice placement was high and the voice shrill.

In the pure cases there is no alteration of the intelligence. The apathy, [mental] heaviness, forgetfulness, that are stated to have occurred in individual cases, may well be referred to the general prostration following several general infectious diseases or perhaps to a slight myxedematous component. We shall again see such manifestations under multiple ductless glandular sclerosis. In pure cases the statements as to alterations of the moral and psychical attitude are on the contrary very frequent; statements that such individuals like early eunuchoids, are psychically more easily excited, and given to sudden anger and to lying. In two cases also has been noted temporary polyuria (*Gougerot* and *Gy*, and *Dalchê*). In the first case the late eunuchoidism came after an acute infectious disease, in the second after lues. We shall often meet with these symptoms in the consideration of multiple ductless glandular sclerosis. Perhaps it is of hypophysial origin.

Are we now justified in separating out these cases as an especial clinical formation and giving it the name "late eunuchoidism?" As has been mentioned, *Gandy* regards them as "dysthyreodie + dysorchidie." *Gallavardin* and *Rebattu* express themselves more in favor of the sexual glands, *Cordier* and *Rebattu* distinguish between an "infantilisme regressif myxedemateux et non myxedemateaux." *Claude* and *Gougerot* finally group all these cases under "insuffisance pluriglandulaire." The confusion can I think readily be overcome if we place in the foreground the classification of these cases according to their etiological factor, and separate out, before everything else, those cases which have the value of experiments, namely, the *traumatic*. Where acute infectious diseases or noxi of a more general nature have led to degeneration of the sexual glands it is very well intelligible that also other ductless glands can suffer damage, and that other features often hard to define become associated with the picture of a disease that is due to falling-out of the sexual gland.

As to the significance of thyroid insufficiency in this disease picture, we can become clear on this point, if we have recourse to the experiments. If in an individual who has attained complete maturity, the thyroid gland is completely extirpated, there come about disturbances of the genital function, but never any such retrogression of the genitalia as has been just described. The thyroprivic disturbance of the genital function can be promptly overcome by thyroidin medication, while all statements are in accord that thyroid medication does not improve the disturbance of sexual glandular function in late eunuchoidism. In spontaneous myxedema of adults the behavior in these respects is not always as clear as in operative myxedema. It should, however, be considered that the disease process that in this condition is responsible for the sclerosis of the thyroid gland very readily and very often involves other ductless glands, and that here we are no longer dealing with mere action at the distance.

Can we show by experimentations the significance of the sexual glands for this clinical picture in a clean and clear-cut fashion? To answer this we must have recourse to the known experiments of *Ancel* and *Bouin*. In male grown animals the ligation or transection of the vas deferens, or pathological stenosis of the exit-ducts of the sperm, leads to degeneration of the germinative part of the sexual glands, while the interstitial substance is retained. The animals become sterile but they are not impotent, and retain their masculine appearance. If, however, the "interstitial glands" are brought to degeneration the animals lose their masculine appearance and become similar to castrates. In this manner there is therefore produced an experimental late eunuchoidism. I refer moreover to late castrates whom I have described above. The same value for the pathogenesis have the very numerous cases of pure traumatic late eunuchoidism; they show that severe injuries of the male genitalia may lead to the full symptom complex of late eunuchoidism; also in these cases there does not exist the slightest basis for regarding the condition as a primary affection of the other ductless glands. The question as to whether the loss of both sexual glands leads regularly to the development of late eunuchoidism does not seem to me entirely solved by the material up to the present time, although I regard it as very likely. *Widal* and *Lutur* have reported a case with marked testicular atrophy, in which the manifestations of late eunuchoidism did not seem to be present. *Cordier* and *Rebattu* discuss the possibility whether in these cases there were still present functionally capable islands of *Leydig's* interstitial cells or ectopic sexual glandular tissue.

Much less clear are the alterations in women. That premature menopause and hyperinvolution of the uterus through repeated births or prolonged lactation does not lead to any change in the secondary sexual characters is readily intelligible, as there need not be associated with the retrogression of the follicular apparatus a retrogression of the interstitial substance.

On the contrary it is really not intelligible why the loss of the whole ovaries exercises such little influence on the axillary and pubic hair. The few cases of pronounced regression of the same seem to me to belong under the caption multiple ductless glandular sclerosis.

The **differential diagnosis** has especially to consider the diseases of the hypophysis that first develop in later years after the attainment of the complete cessation of growth and complete maturity of the body. In this case there is no disturbance of growth, as occurs in the differential diagnosis between the eunuchoid and the hypophysial dystrophia adiposa-genitalis.

Where symptoms of brain-pressure are present and the X-ray shows alterations of the sella turcica, the diagnosis is at hand without anything further. Sometimes difficult, however, is the delimitation from atrophic and inflammatory sclerotic processes in the hypophysis. Perhaps points of differential diagnostic value can be obtained from the examination of the respiratory gaseous exchange and of the purin metabolism. The history also ought to be important; the fact that the patient has sustained a luetic, gonorrheal, or mumps orchitis should at any rate lead to the suspicion of late eunuchoidism. The differential diagnosis with respect to multiple ductless glandular sclerosis has to be considered later.

The *treatment* has not up to the present yielded anything reassuring. That thyroid medication fails is indeed only too comprehensible. But also the administration of sexual glandular substances has led to only transitory results, or, as in the case of *Dalché*, led to improvement of symptoms that probably were not to be referred to the lack of the sexual glands (forgetfulness, general weakness, chills). In the valuation of therapeutic results, we should not forget that in certain cases spontaneous improvement is possible, such as also occurs in early eunuchoidism.

## 5. Treatment of Sexual Glandular Insufficiency

The drug therapy of sexual glandular insufficiency has as yet had in man no decisive results. The feeding with testicular substance is but little carried out, and the reports as to the result of injection of sexual glandular extracts disagree. Spermin (*Poehl*) may have a certain stimulating action on the nervous system, but profound symptoms of insufficiency are hardly improved thereby.

In want of a better treatment, thyroid treatment has been recommended —a therapy that plays a part in the treatment of all ductless glandular affections, in part indeed erroneously. In eunuchoid obesity, thyroid medication has mostly a right good result and is certainly to be recommended if it be employed with necessary caution. It is also conceivable that through stimulation of metabolism often a certain furthering influence is exerted on the sexual glands, but we cannot expect decisive results as to this point. In such cases treatment with hypophysis tablets seems to be entirely valueless. I do not know whether anybody has as yet employed pituitrinum infundibulare. As I have mentioned already, perhaps employment of radium emanations would be of some value, but as yet no experiments with them have been reported. I shall not go further into the question of the other roborant and tonic treatment methods.

The organotherapy of the symptoms due to loss rest on a much broader experience as far as is concerned with woman. The medication with ovarian substances was introduced by *Regis* and has been especially recommended by

*Jacobi*, *Chrobak*, *Landau* and *others*. Various preparations have come into the market; oophorin tablets, ovaraden, ovarin, ovarial tabloids, etc. Ordinarily 3 to 6 tablets are administered daily. As has been mentioned, *Löwy* and *Richter* found in their experiments a stimulation of the respiratory metabolism; but this result seems to be inconstant, as other investigators did not find it. Also there did not always occur an improvement in the nervous symptoms. *Bucura* points out that this may be due to the unreliability of the preparations used. He believes that it is not a matter of indifference whether the preparations are obtained from the ovaries of young or old animals, and whether they are taken during the rutting season or the interval. He mentions experiments with the milk of rutting animals. As yet the involution of the uterus after castration cannot be prevented by the use of ovarian substances (*Jentze* and *Beutner*). *Fränkel* proceeding from his view that the corpus luteum possesses an internal secretion, has introduced lutein tablets into therapy.

Very promising are the experiments on transplantation of the sexual glands. *Ribbert* was the first who succeeded in transplanting testicles. *Foges*, after autotransplantation of the testicles in young fowls, saw rather good development of secondary sexual characters. *Steinach* succeeded with the same experiment in rats and guinea-pigs. The interstitial cells and the Sertoli's cells were retained, but seminal cells were entirely absent. I do not know whether homiotransplantation of the testicles has succeeded. If it were to succeed, a favorable influence on eunuchoidism would not be impossible. The transplantation of the testicles, epididymis and vas deferens and therewith the possibility of semen production is still the task of the future.

Much more noteworthy are the experiments with transplantation of the ovaries. Here also the successful experiment is that of autotransplantation which was done by *Ribbert*. *Knauer* then showed that in grown rabbits involution of the uterus could be prevented by the autotransplantation. An essential progress was made by the experiment of *Halban*, who in new-born guinea-pigs transplanted the ovaries under the skin. After one and one-fourth years there was still present function-capable parenchyma. *Graafian* follicles and even mature ova had development and the tube that had been transplanted at the same time had matured in normal manner. The breasts, as well as the uterus, had developed normally. In the castrated control animals the breasts remained rudimentary and the genitalia were markedly hypoplastic. In woman also has transplantation occasionally been followed with good results in operations on the genitalia. It is true that transplants often show regressive manifestations, but a part of the parenchyma may, however, still be retained, and on account of this the involution of the uterus and the nervous symptoms due to the loss are prevented. In autotransplantation in the neighborhood of the tube, even maturation of the ovum and pregnancy have occurred.

Still more significant are the experiments with homiotransplantation of the ovaries. I refer to the collected statistics of *Novak*. It is true that in most cases the result lasted only for a short time, but in animal experiments numerous results of longer duration including maturation of the ovum and conception have occurred. On experiments in man, I mention the two cases that follow. *Cranner* transplanted into a twenty-one-year-old woman, who had never menstruated and who possessed rudimentary mammæ, the ovary of an osteomalacic woman. Menstruation then set in and the breasts developed. Still more remarkable is a case of *Halliday-Crom*. In this case amenorrhea had set in after labor and symptoms of absence developed. The small cystic ovaries were removed and a foreign ovary implanted. Four months after the operation menstruation occurred for the first time and four years after the operation occurred conception and a normal birth. This case was earnestly discussed before the Edinburgh Obstetrical Society, and cannot well be denied. There is indeed in this case no doubt that if error of observation has not occurred, this woman bore the child of another woman. Serious objections might be raised against such procedures on ethical and forensic grounds.

## III. HYPERGENITALISM

**Definition.**—We have come to know hypergenitalism already in the chapters on the hypophysis and in the consideration of suprarenal cortical tumors. There are also cases of premature development of the genitalia associated with temporary excessive development of the organism, in which the epiphysis or the suprarenal cortex do not come into consideration as etiological factors, but in which we must assume, with great probability, a primary disturbance of the sexual glandular function on the sense of a premature occurrence or an excessive increase.

**Pathologico-anatomical Findings.**—A portion of these cases show malignant tumors of the sexual glands. *Neurath* collects five cases from the literature, four ovarian tumors (two established at autopsy, two on operation) and one testicle tumor (operation). In another the sexual glands were described as only extraordinarily large. I must state that in two cases hydrocephalus was reported. One of the cases was reported by *Wetzler;* also in a case of *Pellizzi's* did there exist, besides pronounced hypergenitalism and excessive growth, hydrocephalus with convulsions. Whether these were cases of primary hypergenitalism cannot in the present state of our knowledge be answered.

**Symptomatology.**—The premature sexual development is found in both boys and girls. *Neurath*, who has written an excellent essay on this subject, quotes forty-three cases of premature sexual development in *boys*. In such individuals an excessive development of the genitalia may occur already in the first year of life.

I quote the following examples. The case of *Bernhardt-Ziehen* was that of a three-year-old boy in whom an enormous growth had set in at the eighteenth month. At two years the pubic, axillary and beard hairs were present. At two and one-half years the legs had hair on them; he was 103 cm. tall, the circumference of the skull was 53 cm., the body weight 49.5 kg. He looked like a seven- or eight-year-old boy. He was again examined at the age of eight years. He was then 138 cm. tall (116 cm. is the height for this age). The circumference of the skull was 56.5 cm. The sexual parts were developed like those of a grown man. He looked as if he were twenty-five to thirty years old. His intelligence was fairly well developed, he was lively, showed inclination for the female sex, but otherwise his demeanor was childish. As another example I cite the case of *Hudovernig* and *Popovicz*. In a later investigation of *Hudovernig* the boy was five and one-half years old; at one and one-half years he sustained a febrile disease (meningitis). The abnormal growth had existed since that time. He was 137 cm. tall and weighed 35.5 kg., this corresponding to the age of fifteen or sixteen years. The penis is 9 cm. long, the testicles very well developed. The psyche is infantile. The intelligence is rather behindhand. Skull and face were rather asymmetrical. The X-ray examination showed that the ossification was as well advanced as that of a fifteen- or sixteen-year-old boy. Also the skull bones were well developed, and the sella turcica seems to have been enlarged, although the observation is not convincing. The boy was first treated with thyroidin tablets or with thyroidin tablets plus potassium iodide. This did not affect the excessive growth. Later ovarian tablets were administered. This time the growth was somewhat less (only 3.1 cm. in nine months as compared with 5 cm. in the six months of the first period and 5 cm. in the ten months of the second period). In the third period the boy seemed to have become psychically more quiet. *Hudovernig* assumes that the ovarian tablets have retarded the excessive growth. I doubt this. If we calculate the growth per month we obtain for the first period 0.95 cm., for the second, 0.5 cm. and for the third, 0.3 cm. There is hence found a gradual decrease of the excessive growth, which surely, as we shall see later, is to be referred to the gradually ensuing closure of the epiphyses. Finally I would mention the case of *Stone*, which is especially interesting from the fact that also the father of the boy showed a premature development.

These cases all have in common the premature and excessive development of the genitalia and of the secondary sexual characters, premature change of voice, and the excessive body development. Already in the first year there occur erections, ejaculation—*Pellizzi* demonstrated spermatozoa in his cases—and eventually premature sexual instinct. The development of the internal genitalia often hurries the development of the whole body. As far as the latter is concerned, the osseous system and the musculature are mostly affected in like manner. There therefore occurs a transitory gigantism; as, however, the epiphysial closure is rather hastened, the body growth finally attained is not abnormal, but mostly rather small. The psychic and intellectual development of such individuals do not keep pace with the body development; they for the most part show a childish demeanor, corresponding with their age, which demeanor has a characteristic stamp only through the premature sexual life. The assumption of such cases as primary hypergenitalism is often uncertain without autopsy findings, although such a primary hypergenitalism may be made secure by operation in certain cases. I mention especially the case of *Sacchi*. It was that of a nine-year-old boy who had developed normally until his fifth year; in that year an excessive growth and especially a premature development of the genitalia and of the secondary sexual characters set in; at the same time there developed a tumor of the left testicle; at nine years of age the boy weighed 44 kg. and was 143 cm. tall. The *lower length* was 77 cm. Hence the boy showed childish dimensions, being thus different from other true gigantism which, as we shall see later, shows either normal or eunuchoid dimensions. The testicular tumor, which was an alveolar carcinoma, was removed. One month after the operation the beard hairs fell out and the abnormal hairiness of the extremities retrogressed; the hairs on the mons Veneris remained. The penis became smaller, the previously low voice became childish, and the pollutions and erections ceased.

In the *female sex* such cases are mostly described under the title menstruatio praecox. The older literature is found in *Kussmaul* and *v. Haller*. *Neurath* counts eighty-three cases from the literature. The external genitalia develop in an abnormal manner, mostly more strongly than the internal. The secondary sexual characters (hairiness, etc.) and the development of the mammæ are always abnormally premature. As in the male sex, excessive growth of the body is found to be more or less pronounced. Also the dentition, the change of teeth, and the appearance of the bone nuclei and the closure of the epiphysial junctures is premature.

I cite the following: The case of *Geinitz* was one of menstruatio praecox in an eighteen-month-old girl. The uterus had attained the size of a twelve- to fourteen-year-old girl. The case of *Klein*, of menstruatio praecox (two and one-half years), the vulva had grown to the size of that of a fourteen-year-old girl. *Stocker* describes two twin sisters, of whom one had been larger since birth. In the first, menstruation began before the end of the first year. The flow occurred regularly every four weeks, lasting three days. At eight years of age the child had the size and appearance of a twelve-year-old girl; she measured 139 cm. and weighed 34¾ kg., while the twin sister was 121 cm. tall and weighed 20 kg. The case of *Neurath* was that of a six-year-old girl who exceeded in size and weight her eight-year-old sister. The ossification conditions corresponded to those of the tenth or eleventh year. Recently there has been reported a case of *Wolff* concerning a girl four years and one month old. The size had been large since birth. The child had menstruated since the second year. She looks like a seven-year-old girl. The hair of the head is long. The height is 121 cm., the weight 26 kg., the span width 114.5 cm. (hence potentized childish dimensions). The intelligence corresponds to the age. The mammæ are very well developed. The mons Veneris is covered with hair. The ossification corresponds to that of a ten-year-old child. Especially instructive is the case of *v. Haller*. In this the menstruation set in at the age of two years; at the age of eight the girl became pregnant and shortly afterward the excessive growth stopped. She became seventy-five years old. This case shows that premature closure of the epiphyses may also occur in the female sex. Finally the case of *Riedel* shows that also in the female sex may in certain cases a primary hypergenitalism be demonstrated. In this case of precocious menstruation (six-year-old child) the uterus was the size of a seventeen-year-old girl. There was a sarcoma of the ovaries; the sarcoma being removed, the menstruation ceased.

**Treatment.**—Up to the present, the treatment, as far as tumors were demonstrable, has been operative. In many cases, as is shown in the above reports, the results were remarkable. Whether X-ray, radium radiations, or mesothorium irradiations have been tried as yet in certain cases, I do not know. Also in cases without demonstrable tumors it is conceivable that injections of thorium X or actinium X might induce an inhibition of the abnormal sexual glandular development and thus influence the premature development of the organism.

## IV. CHLOROSIS

The circumstance that the beginning of chlorosis always falls at the time of puberty or during the time of maturation of the female organism following puberty, together with the circumstance that in chlorosis are found almost regularly, disturbances in the genital sphere shows that this disease, at least in part, belongs in the chapter on the sexual glands. Opinions are at variance in regard to the nature of the functional disturbances. Therefore I avoid placing chlorosis in one of the divisions of hypogenitalism or hypergenitalism and give it a position by itself.

**Historical.**—*Virchow* on the ground of pathologico-anatomical findings assumed a congenital deficient development of the vascular system. *Immemann* supposed a weakness of the blood-forming organs that is in part congenital and associated with the hypoplasia of the vascular system, and in part acquired and temporary. The disease begins in puberty because at this time especial demands are made in blood-forming apparatus. *v. Bunge* places in the center of the pathogenesis a disturbance in the iron metabolism. The maternal organism gives to the child organism the very great amount of iron. This is stored up not during pregnancy but already at the time of puberty, whereby there occurs a poverty of the blood in hemoglobin. *Zander* regards the cause of chlorosis as a disturbance of the absorption of iron, other authors as chronic constipation, and as gastroptosis through the wearing of tight corsets, etc. Basing his views on the theory of *Immermann*, *v. Noorden* for the first time explains a disturbance of the activity of the ductless glands as essential for the coming into existence of chlorosis. According to *v. Noorden* chlorosis depends on an in part congenital, in part acquired, weakness of the blood-forming organs, in consequence of which there occurs in the period of sexual ripening disturbances in the blood-formation proceeding from the female sexual organs. Normally impulses flow from the female sexual glands to the blood-forming organs. Loss or weakening of the internal secretion of the ovaries leads to chlorosis.

*Grawitz* sees the cause of chlorosis in a disturbance of the relation of liquid interchange between blood and tissues. This depends on deficient function of the vasomotors. He therefore regards chlorosis as a neurosis.

Very recently, *Morowitz*, on the ground of observations in which the rest of the chlorotic symptom-complex is associated with an approximately normal blood condition, upholds the view that the blood-changes in chlorosis constitute only a symptom and not the essence itself of the disease; he points to the frequency of thyroid glandular swelling and believes the cause to be a disturbance in the reciprocal action of the ductless glandular system. *Kottman* observes that there is a deficient iron-assimilation on account of a weakening of the internal secretion of the ovaries. Finally we mention the theory of *Charrin* and *Villemin* that chlorosis is a menstrual autointoxication. *Villemin* assumes in addition that the internal secretion of the corpus luteum possesses hemolytic properties.

**Symptomatology.**—Chlorosis is a disease that inclines very much toward relapses. The first attack of chlorosis usually occurs between the fourteenth and twentieth years of life. Cases of so-called tardive chlorosis (*Hajem, Rieder*) are extraordinarily rare. Lately also cases of infantile chlorosis have been described (*Rist, Hutinel, Stöltzner, et al.*). Because of the uncertain connection of these cases with true chlorosis, *v. Noorden* proposed for these cases the name chlorotoid. Also the connections of the extraordinarily rare cases of conditions similar to chlorosis occurring in the male sex (for example, the cases of *Formanoli, Ferrari, Byrom, Bramwell*) are contested by most of the later authors. *v. Noorden* and *v. Jagič* believe that in such cases we are dealing with sexual neurasthenics who are insufficiently nourished. A great rôle in chlorosis is played by heredity. Often in the same family many sicknesses are found. In rare cases there is observed in the same family simultaneous occurrence of chlorosis and of prepubertal eunuchoidism (*Tandler, v. Noorden;* confer also Observation LI).

Chlorosis usually sets in with a series of subjective complaints; attention is attracted to the color of the face. These symptoms consist in ready fatigability, cardiac palpitations on slight bodily exertions, slight dyspnea, headache, sensations of cold—especially tendency to cold hands and feet—eventually seeing black, flickers before the eyes, ear noises, vertigo, fainting-spells, pressure in the gastric region, nausea, etc.

Examination of the heart often shows in advanced cases slight broadening, soft systolic murmurs, the known humming-top murmur over the jugular, furthermore in a great number of cases acceleration of the pulse, great excitability of the cardiac activity and of the vasomotors. Further is found a marked laxity of the arteries (crural double tone). According to the investigations of *Bihler* and *v. Noorden* there is always a reduction of blood-pressure.

Breathing is mostly somewhat accelerated and superficial, with high position of the diaphragm.

As far as the digestive tract is concerned, should be mentioned that there is frequently a slight degree of hyperacidity. According to *v. Noorden*, constipation is not much more frequent than in normal girls. The respiratory gas exchange is mostly slightly increased. The condition of nutrition is usually not bad. Investigations as to the assimilation limits for carbohydrates gave an increase, or at least no decrease. After the ingestion of 150 gm. of grape-sugar, there never, in the experiments of *v. Noorden* and *v. Jagič*, occurred glycosuria except in one case that at the same time showed symptoms of Basedow's disease. Also *Chatin* came to the same result. It should further be mentioned that not rarely chlorotics show a higher level of their body temperature.

In not very rare cases are there found pigmentations of the skin.

The examination of the urine shows no abnormal constituents. Also the products of destruction of hemoglobin are not eliminated in abnormal amount.

I now enter on a description of the blood findings; on account of the poverty in hemoglobin there comes about in the severe cases a greenish-pale facial color, that has given to the disease its name. There are, however, numerous cases that on account of the reddening of the cheeks make a florid impression. Here the disease is unmasked by a close examination of the mucous membranes and careful examination of the blood. The chlorotic blood-finding is characterized by a relatively very marked poverty of the blood in hemoglobin and a relatively slight reduction of the erythrocyte count. Hemoglobin amounts as low as 50 per cent. are very frequent, and as low as 30 per cent. not rare. When there is high-grade poverty of the hemoglobin there is found more or less distinct poikilocytosis; and in addition isolated nucleated erythrocytes. In the lighter forms the count of the red blood cells is normal or only slightly reduced, only in the severe forms do reductions as low as 60 per cent. occur. In the severe cases the specific gravity of the blood is markedly reduced, while that of the serum is essentially hardly affected. With regard to the leucocytes there is a slight relative mononucleosis.

Recently, as was mentioned at the beginning, *Morowitz* has called attention to the fact that in rare cases that otherwise show the symptom-complex of chlorosis, the blood is found to be normal or nearly normal. Already *Laache* had described such cases, also several statements have been made by *O. Naegeli* and *Grawitz*, while lately *Seiler*, *Groag*, *Dubnikoff* and *others* have described such cases. *Handmann* even found twenty-three cases with normal blood findings among forty-four cases of chlorosis.

It is furthermore very noteworthy that the investigations so far made as to the quantity of blood in chlorosis have shown a plethora. While according to the investigations of *Smith* the total amount of blood in normal individuals is about 5 per cent. of the total body weight, this author found in chlorotics with 29-50 per cent. hemoglobin the blood amount to be 7.5 per cent. and 14.3 per cent. The lower the hemoglobin percentage, usually that much larger the amount of blood. *Plesch* and *Oerum* using other methods came to a like result. It should further be noted that in pernicious anemia *Smith* and *Plesch* found subnormal values.

In connection with this subject it might be well to mention the alterations in the water metabolism that are observed in chlorotics. *v. Romberg*, *v. Noorden* and *Rethers* frequently observed in chlorotics a tendency to the retention of water, while on the other hand we often see under the influence of iron-therapy a rapid loss of weight with moderate polyuria. As has been mentioned, products of decomposition of hemoglobin are not, in chlorosis, eliminated in the urine. Therefore we cannot regard an increased destruction of the blood-coloring matter as a cause of the poverty in hemoglobin.

Not at all rarely the thyroid gland shows a swelling. *Giudiceandrea*, *Archangeli* and *Pastianelli* found it in half the cases. *Handmann* found it in twenty-four times among forty-four cases, three times with distinct Basedow's symptoms. *v. Noorden* and *v. Jagič* report an interesting case in which the development of the anemia was associated with a swelling of the thyroid gland and on a relapse led to an acute Basedow's that lasted for several days. As the statements as to the involvement of the thyroid increase in so astonishing a manner (since the time that attention has been directed to the fact), we must ask ourselves whether the *pseudochlorosis* described by *Fr. v. Müller* does not stand in an intimate relation with true chlorosis. *v. Müller* states that in regions where goiters are frequent, there are not rarely found pale, readily fatigable, girls with abnormally irritable heart-action, in whom manifestation of Basedow's disease later became more distinctly conspicuous.

Finally I come to a description of the alterations of the genitalia, after which I shall add some remarks as to the disease's pathogenesis. I shall try to separate those changes that are due to an alteration of the glands of generation and those to changes of the interstitial glands.

Disturbances of development are found in the genitalia in chlorotics not rarely. Deficient development of the external genitalia, deficiency in the prominence of the mons Veneris, flat nates, small labia majora, while labia minora and clitoris are uninvolved; eventually, narrow vagina, faulty development of the uterus, breasts, etc., are sometimes observed. The statistical reports of *Stieda*, and of *H. W. Freund* and *v. Noorden* show that a relatively larger percentage of chlorotics show such developmental disturbances in more or less pronounced manner. There are undoubtedly a not inappreciable number of chlorotics whose genitalia are developed normally. As especially noteworthy I would emphasize that the hairiness of the genitalia, the mons Veneris, and the axillæ correspond to the age of the individual and further that a delayed closure of the epiphysial junctures and corresponding eunuchoid dimensions of the body is in chlorosis not to be observed. *Tandler* states on the contrary that he has observed very frequently in chlorotics a very frequent premature epiphysial closure, and as a result of this, an especial short leggedness and also that the behavior of other sexual characters point to a certain prematurity.

As far as the function of the generative glands is concerned, almost all the statements are concerned with menstruation, while, as is intelligible, ovulation evades observation. Disturbances of menstruation are relatively very common. I here quote some examples from the statistics. According to *Stieda* only seven chlorotics among twenty-three had menstruated regularly. According to *Otten*, among four hundred forty-eight cases there were only one hundred eighty-six who had menstruated regularly before and during the illness. In the first edition of *v. Noorden's* monograph, 60.7 per cent. of one hundred seventy-three cases showed weakness of menstruation. In the newer statistics of *v. Noorden* and *v. Jagič* that embraces two hundred fifty cases this figure was raised even to 77.2 per cent., and twenty-six of the cases had not menstruated before the onset of chlorosis. There are, however, cases with entirely normal menstruation, and furthermore cases with abnormally strong menstrual hemorrhage. *Trousseau* has described such cases as menorrhagic chlorosis. In such cases the ovaries were found to be enlarged and there was a great abundance of follicles. *v. Noorden* and *v. Jagič* on the basis of their compilation came to the conclusion that in chlorosis menstruation shows no characteristic behavior.

**Pathogenesis.**—If we now survey what I have just said as to the relation of the sexual glands and the primary and secondary sexual characters, we find it hard to accept the theory that chlorosis is a functional disturbance of the interstitial glands, especially if we compare it with those manifestations which are described in the rare cases of female eunuchoidism. There is indeed no doubt that in chlorosis there occurs an enfeebled development of the primary and secondary sexual characters, but in such cases these are mostly only of a slight grade, and just the essential symptoms of failure (deficient hairiness, delayed epiphysial closure) are absent practically always; indeed on the contrary, according to *Tandler*, as has been mentioned, the development points to a degree of prematurity. Also animal experimentations have as yet failed to furnish any support for the assumption of a diminished activity of the interstitial glands. According to the investigations of *Monaro*, *Breuer*, and *v. Seiller* the extirpation of the ovaries in young dogs in a state of development indeed leads to a temporary commensurate sinking of the amount of hemoglobin and count of erythrocytes, never, however, to the blood picture observed in chlorosis. If I here use the methods that I employed in the exposition of the tests of the sexual glands for separating the symptoms that depend on the functional failure of the interstitial glands from those to the functional failure of the generative glands, I may suppose a slight strengthening of the function of the interstitial glands; it is, however, a priori improbable that these stand in the mid-point of the pathogenesis. I believe that there is applicable an hypothesis that at least has the advantage that it is not contradicted by any of the known facts. In chlorosis, as has already been mentioned, the behavior of menstruation shows nothing characteristic. We find in the majority of cases weakening of the menstrual process, however, also a normal course or an essential strengthening. This is what is told to us with regard to menstruation, but not in regard to ovulation. We know only that there is no menstruation without ovulation. It is known however that under circumstances ovulation proceeds without menstruation, and it does not seem to me that anything stands in the way of the proposition that under circumstances it may go on in an increased or precipitate manner. The assumption of precipitate ovulation in chlorosis is, however, though it seems fascinating, not at all unconditionally necessary. To me the assumption seems enough that the violent revolutions that go on in the feminine organism at the time of puberty or with the setting in of a strengthened activity of the follicular apparatus lead in nonvigorous individuals to a temporary or longer continued exhaustion of the organism. We have seen in the description of the physiology of the sexual glandular apparatus that ripening of the follicle in the premenstrual period leads to a heightened vitality of the whole organism. There hence proceed impulses from the follicular apparatus that spur on all the organs and especially the entire ductless glandular system to a heightened activity. Would it not be conceivable that in a predisposed individual, in whom these impulses are perhaps increased by precipitate ovulation, there may appear an exhaustion?

On the basis of this supposition I shall now proceed to analyze the symptom-complex of chlorosis. Let us first consider the genital disturbances. The assumption of an increased activity of ovulation does not seem to me to stand in contradiction to the diverse behavior of menstruation. On the one hand it explains cases with increased menstrual bleeding, and on the other that after a time a feebler organism no longer reacts to every impulse of the growing follicle, or at any rate not with the corresponding alterations of the uterine mucous membrane. It is therefore not at all necessary to consider that the internal secretion of the corpus luteum normally is cast off through menstruation and that with the continued absence of menstruation with progressive ovulation an autointoxication becomes established (*Villemin*). Otherwise we would have to have a chlorosis in every case of amenorrhea, and the cases of chlorosis with excessive hemorrhage would not be explicable at all.[1] An increased activity of the follicular apparatus would also exercise a certain reinforcing action on the function of the interstitial glands, thus explaining unforcedly the symptoms of prematurity that are seen in certain cases.

Through my assumption, a case of childish gigantism with sexual prematurity and chlorosis, observed by *Hastings Gifford*, does not seem so inexplicable. The author had observed this case between the second and the eighteenth years. Menstruation began at the age of thirteen months and from then on came at irregular intervals up to the eighth year of life, after that it was regular. With the menstruation at the thirteenth month occurred also a rapid growth, at three and one-half years of age the child was already 146 cm. tall and weighed 41½ kg. X-ray plates of the hand showed a development that corresponded to that of an eight-year-old girl; the sexual development was that of a thirteen- to fourteen-year-old child. The intelligence had remained somewhat behind. From the sixth to the twelfth year the girl was always under treatment for recurring chlorosis. From then on recovery set in.

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[1] The assumption of *Villemin* depends in addition on the incorrect hypothesis that in chlorosis there is an increased blood disintegration.

We have further seen that in the premenstrual period the activity of the ductless glands is increased, so that there is hence in chlorosis either an increase in the activity of the ductless glands, or, in those whose activity comes most in demand, an exhaustion. Very significant in this respect seems to me the behavior of the thyroid gland. I refer to findings described under symptomatology and the frequency of slight symptoms of Basedow's disease. From this standpoint it is indeed intelligible that a newer attack of chlorosis, that perhaps takes place with the maturation of a follicle, leads, when a corresponding disposition is present, to temporary symptoms of Basedow's disease (see the cases of *v. Noorden* and *v. Jagič*).

A second ductless gland whose activity seems to me to be very significant is the chromaffin tissue. We have seen that under normal conditions there occurs in the premenstrual period an increase of blood-pressure, and we have expressed the opinion that impulses proceed from the ripening follicle that increase the activity of the chromaffin tissue and raise the vascular tonus.

Plainly this organ can become relatively rapidly exhausted, the exhaustion leading to an influencing of the vasomotor system in the sense of an irritable weakness. The laxity of the arteries as well as the low blood-pressure belongs to the constant symptoms of chlorosis. We may indeed go further and try to explain the blood alterations, at least in part, from this point of view. Heightened tonus of the vessels leads to hyperglobulia through transudation of the plasma into the tissue. (I refer to the discussions on the subject of tetany, and those concerning the significance of the chromaffin tissue for the regulation and distribution of blood-pressure.) It is therefore to be expected that on decreased vascular tonus there will be an increase in the amount of the blood; as the blood becomes thereby poorer in erythrocytes, it is to be assumed that erythrocytes that are then poorer in hemoglobin are given off to the blood paths. Just these conditions obtain in chlorosis, increased amount of blood, slightly reduced erythrocyte count, more markedly reduced amount of hemoglobin. In a group of cases the functional breadth of the bone marrow may fully suffice for this regulation, in another group it soon comes, according to this view, to exhaustion and hence to a higher degree of poverty in hemoglobin. In addition to this it is possible that direct impulses go from the follicular apparatus to the bone-marrow and on increased activity of the former favor the exhaustion of the latter. As according to this hypothesis we are dealing only with an exhaustion due to the large demands, it is intelligible why in the few autopsies on cases of chlorosis the bone-marrow was found to be normal (*Birch-Hirschfield, Grawitz*). Perhaps other symptoms of chlorosis point to a lessened valuation of the chromaffin tissue, signs, such as slight mononucleosis, the not rare pigmentation, and indirectly the high carbohydrate tolerance, that up to the present have been observed by all investigators. The investigations as to the blood sugar have not as yet been made. At all events it would not be unintelligible why chlorosis develops just in individuals with hypoplasia of the vascular system, which, as is known, is associated with hypoplasia of the chromaffin tissue; the corroboration of our views would be an instance of the penetrating vision of the past-master, *Virchow.*

This hypothesis seems to me also to explain why chlorosis is found almost exclusively in the female sex. If we were to assume the insufficiency of the interstitial glands, it would be indeed unintelligible why in eunuchoidism, in which the symptoms of insufficiency are so conspicuous, we meet with no chlorosis. The interstitial glands have the same function in both cases; the follicular apparatus is something specific for woman. The revolutions that take place in the female at the time of maturity are different from those that occur in man and are much more powerful.

The experimental basis for this view is yet to be laid. Whether the implantation into young animals of ovaries taken in marked ovulation will be able to produce a picture similar to chlorosis, is at all events questionable; just as castration, which according to the view set forth would bring the chlorosis to a standstill in a short time, is impracticable. We must, however, consider whether a very cautious X-ray irradiation of the ovaries would not act favorably on the chlorotic process.[1] Perhaps this view furnishes the key for the solution of the problem of iron therapy. As is known, iron has an almost specific action in chlorosis, while in the other anemic processes it mostly fails. *Morawitz* has concluded that the iron does not act principally on the bone marrow, but somewhere else in the body. From the stand-

[1] I would here call attention to the later views as to the cause of uterine hemorrhages. *Pankow* pointed out that metritis and chronic endometritis could not be the cause of the profuse menstrual hemorrhages. The chronic inflammation may very well be associated with profuse bleeding, but it does not condition it. *Pankow* seeks the cause rather in a different functional size of the ovaries conditioned by "disturbances in the reciprocal relations of the ductless glands to each other." Perhaps the assumption of a deficient or increased ovulation would suffice, as the climacteric hemorrhages have been favorably influenced by X-ray irradiation (*Döderlein*), which restricts the process of ovulation.

point mentioned, it would be well to investigate whether ovulation or the giving-off of hormones is not inhibited by the great amount of iron ingestion. At all events it seems to me that such a specific influence of iron on the ovaries is not at all necessary. The difference of chlorosis from anemia consists in the fact that the bone marrow in the former is not diseased, but simply gives out because of increased demands, in the course of which exhaustion the formation of the red cells is less affected than that of the hemoglobin. It is thus readily understood why in chlorosis abundant administration of iron works better than in the anemias. With the increase of the hemoglobin may be exercised a favorable influence on the entire organism and indirectly on the sexual glands.

## Appendix. Osteomalacia

In way of an appendix, some remarks as to the relations between osteomalacia and the ductless glands might find place here. There are no doubt a number of, in part, important facts that point to the involvement of the ductless glandular system in the development of the osteomalacic process; the most important of these observations are the following:

1. Osteomalacia occurs almost exclusively in women, and indeed, in the overwhelming majority of cases, during pregnancy.
2. Castration leads very often to a rapid cure or at least a considerable improvement of the osteomalacic process (*Fehling*). Also after labor or after artificially induced abortion, osteomalacia tends to cure or at least to improve, just to relapse at the next pregnancy.
3. The curative or ameliorative action of castration can in such cases enter in without the interruption of the pregnancy (cases of *Cramer*, *Walcher*, *Cristofoletto*).
4. Frequently symptoms are found in osteomalacia that point to an involvement of the other ductless glands. Thus for instance osteomalacia is not rarely complicated with Basedow's disease (*Latzko*), or with Basedow's and tetany (*Köppen*, *v. Recklinghausen*). *Möbius* reports a case of Basedow's that later went over into myxedema, and then later acquired puerperal osteomalacia. Moreover there is found in osteomalacia frequently, perhaps regularly, a hyperplasia of the parathyroids (*Erdheim*, *Strada*, *et al.*). This hyperplasia of the parathyroids does not tend to occur in senile osteoporosis.
5. In osteomalacia the glycosuric action of adrenalin and apparently also its action on the heart and vessels is strikingly slight (*Cristofoletti*, see also *Reinhardt*, *Merletti*, *v. Neusser*, *Engländer*, *et al.*). This is also true for osteomalacia during pregnancy, because otherwise in pregnancy the action of adrenalin is especially powerful. Furthermore, long-continued injections of adrenalin in many cases of osteomalacia have exerted favorable influence (*Rossi*). *Cristofoletti* has

collected forty-seven cases of osteomalacia that were treated with adrenalin. Of these, eleven were gravid and thirty-five nongravid women. Of the gravid women 45 per cent. were cured, and about 18 per cent. improved. Of the nongravid women about 17 per cent. were cured, and 40 per cent. improved.

6. In some cases of osteomalacia improvement follows the injection of pituitrinum infundibulare (*Bondi*, *Pál*). Lately *Pál* has reported concerning excellent influencing of the osteomalacia, in two cases, through injections of pituitrinum glandulare.

Three *forms* of osteomalacia are to be distinguished. The *puerperal* form which is by far the most frequent. The *rheumatic* form, which is rare, which mostly does not follow a severe course and which occurs also in women independent of a preceding labor. It is also observed in man. Finally the *senile* form.

The views as to the bone processes in osteomalacia are many. One group of authors impart the most important value to the decalcification of the completed bones, another group to the apposition of especially calcium-poor bones. Likewise is there division of the authors as to whether rachitis and osteomalacia are two different disease conditions or constitute one and the same disease process, that leads when it develops in youth, to rickets, and when it develops in the fully developed organism to osteomalacia. *Cristofoletti* sets forth the facts that speak against the unitary theory, as well as gross anatomical difference: the endemic occurrence of osteomalacia that is independent of the extension of the rachitis, the occurrence in grown people, and finally the cardinal symptom of osteomalacia, the pain, which is absent in rachitis. The fact also seems to me noteworthy that rachitis mostly affects persons who were not rachitic in youth.

As might be expected, investigations as to calcium metabolism in osteomalacia show great disturbances. Almost regularly is found negative calcium equilibrium. Especially is the elimination of calcium through the intestine increased. That therewith the phosphorus is also eliminated in increased amount in the feces is not characteristic for osteomalacia, as the calcium carries with it the phosphorus. The calcium contents of the blood in osteomalacia is somewhat raised (*Capellani*). We can see a certain relation between pregnancy and osteomalacia in that fact that osteophytes that normally form during pregnancy are very poor in lime.

Of the hypotheses that are at hand as to the pathogenesis of osteomalacia, I mention those only that concern the ductless glands. The assumption of a specific thyrogenic disturbance cannot be accepted as correct, nor can the view that goiter formation and the osteomalacia have a causal connection. Among thirty-four cases of osteomalacia, *Bossi* saw not one with a goiter; and I can also very well reject the supposition of a primary functional disturbance of the chromaffin tissue. The sexual glandular hypothesis has attracted the most adherents. Through the favorable results of castration, *Fehling* was furnished the occasion for seeing the cause of osteomalacia in a hyperfunction of the ovaries. *Cristofoletti* modified this hypothesis by assuming that the internal secretory function of the ovary lasts during pregnancy, and that this leads to a hypofunction of the chromaffin tissue.

For an especial functional disturbance of the interstitial glands speaks the finding of *Wallart* that the interstitial substance in osteomalacia is especially strongly developed. The assertion of *Siegert* and *M. B. Schmidt* that infantilism and osteomalacia belong together is made scarcely plausible by this fact alone. As, however, also in normal pregnancy the interstitial glands are more strongly developed, it is questionable whether we may estimate the value of the findings of *Wallart* as high, although I am unable to bring anything else against them.

I would not ascribe to the hypofunction of the chromaffin tissue so great a value as does *Cristofoletti*. As signs of it, *Cristofoletti* quotes: the hypereosinophilia, the absence of the adrenalin glycosuria and the eventually present pigmentations. Why then, however, do we never find osteomalacic manifestations in Addison's disease? The combination of hypofunction of the chromaffin tissue with pregnancy can then very well not be so full of importance, for finally there are cases of osteomalacia without pregnancy. Moreover the relations of the chromaffin tissue and metabolism are still right questionable.

As for a continuance of ovulation during pregnancy in osteomalacia, there are to my knowledge no observations at hand. After all, the assumption of a hyperfunction of the ovaries is up to the present the only one that can be supported by numerous and good observations. It is at all events surprising that the osteomalacic process is as well influenced by both castration and by normal or artificially induced labor. We may, however, suppose with *Halban* that the activity of the ovary and that of the chorionic epithelium become summated, and that it is therefore sufficient to limit only one of these factors. Also the hyperplasia of the parathyroids perhaps finds explanation by this hypothesis. Already during normal pregnancy are greater demands made on the parathyroid glands, still greater demands may lead to hyperplasia (confer the chapter on the parathyroid glands).

The observations of *Pál*, that extracts of the anterior lobe of the hypophysis influence osteomalacia favorably, turn the attention to the hypophysis. Perhaps in osteomalacia the normal hyperplasia of the anterior lobe during pregnancy fails to take place. Up to the present, all these theories are hypotheses, as between the described and the supposed alterations in the function of the ductless glands and the profound disturbance in the osseous system a very wide gap still yawns.

In a thorough monographic dissertation on osteomalacia and rachitis, *G. Pommer* has upheld the view that both diseases depend on an affection of the central nervous system. Considering the intimate relationship between the central nervous system and the function of the ductless glands this supposition seems to me to deserve more attention than it has thus far found.

## Addendum

*Whitehead* reports the histological examination on the testicle of the case of *E. M. Prince.* As *Prince's* case is very interesting and apparently forms the only case on record of true human hermaphroditism in which the organs of both sexes were present, it will be quoted in extenso:

The patient, apparently a girl, eighteen years of age, consulted Dr. Prince stating that she had never menstruated, and that she suffered from headaches supposed to be due to that fact; she had withdrawn from the college she had been attending because of the headaches which were worse about every twenty-eight days. She appeared to be a healthy, robust girl, refined and intelligent. There was a heavy growth of hair upon the head, the voice was soft and feminine and the breasts well developed, rather larger than ordinarily seen in a girl of her age. The hips were typically feminine, the mons Veneris was rather scantily covered with hair, the labia majora were normal; the clitoris was not enlarged and the hymen was unruptured. No uterus could be made out by rectal examination. The vagina was about 2 in. long, and terminated in a blind pouch. In the upper part of each labium majus a body could be felt which was freely movable. The diagnosis made was congenital abscess of the uterus with hernia of both ovaries. At the operation (exploratory laparotomy) a small body the size of a pecan nut was found at the usual site of the uterus, and to the left of this there was found an apparently normal ovary with a rudimentary tube. At a subsequent operation the two bodies in the labia majora were removed and were found to be testes, a diagnosis which was afterward confirmed by a pathologist.

In this case the secondary sexual characters were of the female type. A weak point in the case is the absence of the microscopical examination of the bodies believed to be ovaries.

*Saenger* reports seven cases of eunuchoidism which had come under his personal observation, and concludes that the condition is by no means so rare as is generally supposed. His last case is especially interesting in that the subject was an kyphoscoliotic acromegalic individual aged thirty-three years, who developed a late eunuchoidism in consequence of a gangrene of the testicle; after the injury there was a failure of potency, a falling-out of the hairs of the beard and pubic regions—and in part also of the eyebrows—but there was no eunuchoidal distribution of fat, or gigantism.

All references to the subject of the sexual glands would be incomplete without mention of the name of *Leo Loeb*, whose researches on the function of the corpus luteum are epoch-making. According to *Loeb* the corpus luteum supplies to the uterus a sensitizing substance which prepares it to respond with the production of the maternal placenta, if there is added an external stimulus of mechanical nature.

*Whitehead* (*R. H.*). The structure of a testis from a case of human hermaphroditism. Anat. Record, Vol. VII, 1913, p. 83.

*Saenger* (*A.*). Ueber Eunuchoidismus. Deutsche Zeitschrift für Nervenheilkunde, Vol. LI, H. 3–6, 1914, pp. 178–197.

*Loeb* (*L.*). The experimental production of the maternal placenta and the function of the corpus luteum. J. Am. M. Ass., Oct. 30, 1909, Vol. LIII, No. 18.

## CHAPTER XI

# PLURIGLANDULAR DISEASES

### Multiple Ductless Glandular Sclerosis.—Gigantism

It was already in the first chapter pointed out in detail that in recent time there has been a growing tendency especially in the French literature to regard individual diseases of the ductless glands as pluriglandular diseases. The number of contributions as to pluriglandular disease has shown a steady growth. I have already stated my opinion that I regard this tendency as mistaken. It must have the result that the individual typical disease pictures will become more and more confused and that the laborious acquisitions [to our knowledge] will again become lost in the general chaos. In order to make manifest my viewpoint on this question, I would again briefly capitulate what I have already stated in detail in the first chapter as to the physiological and pathological correlations. The disease of an individual ductless gland regularly has as a sequel disturbance in the other ductless glands, that eventually may be recovered from if the gland primarily affected becomes healthy or if, for example, its absence of function [Ausfall] has become covered by therapy (physiological correlations). By pathological correlation I mean the phenomenon that the disease that has first involved one gland commonly, in its further course, involves other members of the ductless glandular system. Here also in the majority of cases may be established what ductless gland was first involved; for the most part indeed the disease of the ductless gland stands so much to the fore, that in this case also I would rather avoid the designation pluriglandular disease. Much more do I consider it correct to reserve this term for those cases in which from the clinical picture it must be concluded that the disease process embraces the whole ductless glandular system or at least a large part of it. *Multiple ductless glandular sclerosis must be designated as such a pluriglandular affection* Κατ' ἐξοχήν. In such cases we have to deal with general symptoms of deficiency [of function, Ausfallerscheinungen] on the part of the system of ductless glands.

The question as to whether the antitype exists, that is, if there occurs a generalized hyperplasia of the ductless glandular system with corresponding manifestations of increased function, seems to me not yet ripe for discussion. There is no doubt that hyperplastic changes in the thyroid gland and in the suprarenal cortex are not rarely a concomitant of acromegaly. But in this case there is no occasion to doubt the diagnosis acromegaly on this account. So much is the picture dominated by symptoms on the part of the hypophysis. The only disease that perhaps belongs here is *gigantism.* Later I shall expound in detail that I cannot regard gigantism as simply an acromegaly of child-life, as *Launois* and *Roy* assert. The enormously increased tendency to growth of the entire body seems to signify to me much more a *rendering potent of the entire ductless glandular system,* that is mostly followed by a rapid exhaustion, in which some glands, as for example the sexual glands, even at the beginning of the disease, show signs of a decay [of function] or of a remaining backward in development. One aspect of the problem seems to me not as yet explained, namely, whether we are justified in regarding the potentizing of the ductless glandular system as alone the cause of the increased tendency to growth or whether we must not assume that from the beginning there was an abnormal tendency [mapping-out, Anlage] of the entire organism, including the ductless glands. It seems to me, however, that the inclusion of gigantism among the pluriglandular diseases seems best adapted for our purpose.

## Multiple Ductless Glandular Sclerosis

**Historical.**—A portion of the cases that I shall group under this term appear in the literature under very diverse designations. In the description of late eunuchoidism it was mentioned that the cases of multiple ductless glandular sclerosis all are associated with more or less distinct symptoms of late eunuchoidism, that however these symptoms constitute only a partial manifestation of the picture far richer in symptoms of multiple ductless glandular sclerosis. A uniform conception of this disease picture has not as yet permeated the French literature. *Gandy* describes as infantilism reversif ou tardif a part of the cases here set forth by myself and ascribes an important etiological factor to a disease of the thyroid gland. *Cordier* and *Rebattu* place the sexual glands as the central figure of the pathogenesis and distinguish between dysorchidie and dysorchidie-dysthyroidie. The works of *Claude* and *Gourgerot* mark an essential advance, these authors in 1907 having described this clinical picture under the terms insuffisance pluriglandulaire endocrinienne. To my mind, however, *Claude* and *Gourgerot* have lately gone too far, in that they and especially also later French authors have included under this designation cases whose position [thereunder] have seemed to me uncertain. I have already dealt with this in detail in the first chapter. There I have classified together under the term multiple ductless glandular sclerosis those cases in which a primary simultaneous disease, or almost simultaneous disease, of several glands exist cases that we must regard as correlated to the inflammatory sclerosis and atrophy of the ductless glands as found at autopsy.

There are, of course, cases of spontaneous myxedema or of Addison's disease that likewise depend on inflammatory sclerosis of the ductless gland concerned. Mostly, however, we are in a position sharply to differentiate the disease pictures. In the cases about to be described however we are dealing with a symptom-complex that already in vivo suffices to let us refer the diagnosis to a more or less generalized sclerosis of the ductless glands and justifies us in picking out this disease-form as an entity.

**Definition.**—*As multiple ductless glandular sclerosis I term that clinical picture which is brought about by a probably infectious, for the most part not as yet more well-defined, disease process—a disease process that involves several ductless glands simultaneously, and leads to high-grade sclerotic atrophy and hence to manifestations of deficiency on the part of these glands. Thyroid gland, sexual glands, hypophysis, and suprarenals are mostly involved. Correspondingly are found more or less pronounced the manifestations of hypothyrosis, of late eunuchoidism, and hypophysial insufficiency, combined with a syndrome similar to Addison's disease (hypotonia, pigmentations, etc.). Especially brought into prominence is a progressive [i.e., uncontrollable] cachexia, that develops to a high grade.*

**Case Histories.**—Of the cases reported in the literature I regard the following as belonging to multiple ductless glandular sclerosis. At all events I must mention that some of these cases are not exactly enough described, so that their membership in the group is not quite certain.

*Observation of Rumpel.*—Man, thirty-six years old. Great weakness, backs of hands and feet thick and puffy, pronounced cachexia, and considerable anemia, skin dry, weakness of memory, frequent chills, temperature abnormally low, penis of normal size, scrotum very small, testicles much atrophied, but still sensitive. Cremasteric reflex weakened, libido absent. Hair in the axillæ, on the pubis, etc., scanty; also the hair of the head is thinned out; subcutaneous fat-tissue increased, especially on mons Veneris; polyuria and polydipsia, gonorrhea at the age of twenty-four years. Beginning of the disease in the thirtieth year of life with gradual loss of the sexual instinct, with thickening of the skin of the dorsa of the hands and feet, lessening of memory, falling out of hair, etc. Thyroid treatment without result. No autopsy.

*Observation of Ponfick.*—Man, forty-seven years old, cobbler, married since twenty-third year of life, has six children. Since the thirty-second year has had a gradually-increasing fullness of the face, working ability decreased, the cheeks become puffy, the lips swollen, the skin rigid and pale as wax, the hair of the head thinned out, the hair on the cheeks is entirely absent. Also the mustache is thinned out. Mimicry slow, speech scanning, hearing diminished, skin slightly colored cyanotic, scaly, the hairiness of the trunk and extremities has decreased markedly, the genitalia are almost entirely devoid of hair. Hemoglobin 55 per cent. Essential improvement on thyroid medication, gain of weight, 8 kg., hemoglobin rises again to 75 per cent. In spite of continuation of the thyroidin treatment, later much puffiness of the face, diarrheas, hemoglobin again falls, hearing becomes worse (sclerosis of the middle ear), body weight sinks lower, although thyroidin is no longer given. Death from pneumonia. Thyroid 10.2 gm., therefore only a third of the normal weight. The isthmus and the parts bordering on it well retained, however, and show tissue that is entirely capable of functionating. Periarteritis hemorrhagica. Suprarenals generally thinned, cortex somewhat smaller. Hypophysis: in the sella turcica a large cavity, the posterior lobe well retained, the peduncles of the hypophysis penetrate the cavity (hydrops ex vacuo), dura grown fast to the underlying tissue. Destruction of the glandular lobe. Callous thickening in the retained part. Rigidity of the fiber masses.

*Observation of Gouilloud.*—Woman, thirty-seven years old, mother of three children, severe hemoptysis at the thirty-third year, at that time cessation of menses, which have never been right since that time; the temperament, which was formerly very lively, has altered, the patient is apathetic, forgetful, childish mentally. Cachexia for the last half year. Face pale. Lashes have in part fallen out. Also the hair of the head is thinned out and has lost its color. Also the hairs of the axillæ and on the pubis have fallen out. The hands are cold, backs of the hands edematous. The thyroid is apparently smaller than normal, the uterus entirely atrophic. Improvement by thyroid therapy doubtful.

*Observation of Djemil Pascha.*—Man, eighteen years old, testicles began to atrophy three years ago, the potency became lost. The mamillæ began to increase in volume, also the breasts became larger, the pitch of the voice was higher. After operative removal of the breasts libido returned, the testicles became larger again, pollutions occurred; later, increasing paleness and puffiness of the skin of the entire body, apathy, increasing cachexia, dryness of the hair. Medication with thyroidin unsuccessful, death, no autopsy.

*Observation of Claude and Gougerot.*—Man, forty-seven years old, formerly very potent, father of three children, alcoholism. At forty-two years, probably tetany, also perhaps nephritis. During convalescence falling out of the hair of the head, the testicles atrophied, complete impotence, the voice altered, and also the external genitalia became atrophic. Hairs of the beard very scanty. Pubic hair and axillary hair absent. Skin dry, apathy, pigmentations on the skin and mucous membranes, low blood-pressure, asthenia, gradual diminution in the size of the thyroid gland, high-grade cachexia, tuberculosis of the lungs, death. Autopsy showed tuberculous foci in lungs, liver and kidneys. The thyroid very small, only 12 gm. The testicles very atrophic (22 gm.), prostate and seminal vesicles also atrophic. Hypophysis small and sclerotic. Histological examination of the skin; atrophy of the epidermis; hair follicles, sweat glands and sebaceous glands atrophic.

*Observation of Gandy.*—Man, thirty-three years old, formerly gonorrhea, father of two children; was very potent; at twenty-seven years, polyuria, headache, severe sweats, puffiness of the face, falling out of hair, nasal hydrorrhea. Later retrogression of the secondary sexual characters and atrophy of the genitalia. Looks like an eighteen-year-old youth. Skin of the face, pale, subicteric, skin dry, slightly scaly. Hairs of beard very scanty. Trunk and extremities bald. Scrotum and testicles quite small, the latter insensitive. Penis 6–7 cm. long. Complete impotence. Prostate also atrophied. Cremasteric reflexes absent. Perineum and genitalia have lost their pigment. Autopsy: Inflammatory sclerosis of the thyroid (7 gm.), the testicles very small (8–10 gm.). Interstitial substance has disappeared entirely. Meningitic changes at the base of the skull, with edema of the brain. No statement as to hypophysis.

*Observation of Brissaud and Bauer.*—Twenty-nine-year-old woman, heart failure, embolism, tuberculosis, peritonitis. First menses at the age of fifteen. Birth of child at the age of twenty. From that time has not menstruated. Infantile appearance, face very pale, slightly swollen, breasts little developed. Hair of head dry and thinned out, likewise the eyebrows, entire absence of pubic and axillary hair. Voice monotonous. Apathy, headaches, anemia, and cachexia. Autopsy. Thyroid 15 gm. apparently normal. No statement as to microscopical examination. Left side salpingitis and oophoritis. Right ovary much sclerosed, very small. Uterus like that of a little girl. No statement as to the pituitary.

*Observation of Sainton and Rathery.*—Woman, thirty-two years old, syphilis at the age of twenty-five. Very distinct myxedema, appears very infantile, absence of pubic and axillary hairs. Hair of head thinned out, dry. Apathy. Speech slow, almost complete amaurosis, pulse 66, improvement as a result of thyroidin medication. Autopsy. Thyroid gland sclerosed, 12 gm., thymus large, suprarenals sclerosed. Genitalia atrophic. Ovaries very small, sclerotic. Uterus infantile. Soft malignant, cystic degenerated tumor of the hypophysis.

*Observation of Josserand.*—Man, thirty years old, five years ago influenza and articular swellings, later great loss of body weight, marked weakness, the mustache fell out, also the axillary hair and the eyebrows, the skin of the penis became thick, and inelastic, atrophy of the testicles, loss of libido and of potency. Extreme weakness, then some improvement. Anemia, senile appearance. Testicles the size of hazelnuts, bilateral hemianopsia, apparent increase in size of the hands and feet.

*Josserand* mentions in brief a second case who at the age of thirty-five passed safely through an attack of influenza, and later became senile.

*Observation of Gougerot and Gy.*—Man, fifty-two years old, formerly very strong, very potent, at the age of forty-one years a "hard to define" infectious disease, with pains in the limbs and in the abdomen, vomiting and numbness, lasting two and a half months. Later asthenia, and temporary polyuria. From this time on libido and potency gradually lessened and finally disappeared. Hairs of the beard fell out, axillary and pubic hairs are almost entirely absent. Senile appearance, testicles atrophied, sensation of cold, tuberculosis of the apices, lupus on the nose, erysipelas, later pneumonia. Autopsy: Thyroid gland highly sclerosed, right lobe 6 gm., left lobe 5 gm. Testicles likewise sclerosed, right 18 gm., left 20 gm. Suprarenals sclerosed, chiefly in the cortex; pancreas also sclerosed, likewise the hypophysis (0.3 gm.), and the parathyroids. Also liver, spleen and kidneys sclerotic.

*Personal Observation.—Observation LIII.*—Forty-year-old man (history partly elicited from the wife of the patient). Father of the patient died at the age of sixty years of carcinoma of the stomach, mother at forty-five years, of tuberculosis. One brother also died of tuberculosis, otherwise no tuberculosis in the family. One uncle died of diabetes. No gout, no obesity, no Basedow's in the family. The patient himself had in his youth passed through measles and scarlet fever. At twenty years of age, catarrh of the pulmonary apices, that became healed. The patient then remained healthy up to his thirty-fifth year. Sexual life was fully normal. He married at the age of twenty-eight years and has three healthy children. Hair of the head abundant, and there was a fair amount of hair on the trunk and extremities. Abundant beard. Axillary and pubic hair abundant. Potency and libido entirely normal. Had never engaged in [sexual] excesses; at the age of twenty-two years gonorrhea and slight orchitis. He was never especially strong muscularly, was always rather thin, but he felt well and could always fulfill his now and then exacting duties as a tradesman. At the age of thirty-five years he became ill rather acutely with fever, lancinating pains in the extremities, pains in the back and neck (he cannot say whether the thyroid was swollen). The physician diagnosed influenza and ordered aspirin. For some days later there also existed diarrhea. The fever rose as high as 39.5° C. Later when the acute manifestations had retrograded, there occurred edema of the legs, the face, and also the backs of the hands and feet. Albumin was found in urine and the physician assumed a nephritis. The patient felt very weak, after about eight weeks improvement occurred, but the weakness persisted; convalescence continued for an unusually long time, for several weeks still the patient suffered from great muscular weakness, he became thin, and the edematous swellings disappeared very slowly. After three months the patient had recovered, yet he never felt entirely well since that illness. The potency gradually became lost, and about three-quarters of a year after the illness the testicles seemed to him to be smaller. Also the penis was smaller, the hair of the head had become thinned out immediately after the illness, so that some bald spots had formed. Now began also the hair of the mustache and beard to fall out, and the axillary and pubic hair, and the hair on the trunk gradually disappeared. Since this time the patient has been an invalid. The physicians had later assumed healing of the nephritis, however, the puffiness of the skin had never been lost entirely. The patient is very apathetic, tires very easily, shivers, is never quite warm, has never attained his former body weight, mental work exerts him very much, he sleeps poorly at night, suffers from pressure in the head, sometimes complains of drawing pains in the back and legs; lately the swelling of the face has again become distinct. Also the pallor of the face has increased. He has visited different bath resorts and taken many medicines, among them iodine and arsenic. The bowel movements often occur at intervals of four to five days. Recently, albumin has again been found in the urine.

The patient came under my observation in May, 1911. Medium height, cachectic appearance, looks very much older. Face pale with a light yellowish tinge. Distinct puffiness of face, especially about the eyes, on the cheeks and lips. Light livid discoloration of the middle of the cheeks. On the upper lips mustache hairs very scanty only; chin and cheeks bald. Hair of head thinned out, dry, and brittle, at certain places much more scanty, especially on the occiput. The trunk is bald, there are no hairs in the axilla; at the root of the penis a few scanty hairs only, the perineum is almost free from hair. Tongue perhaps somewhat thickened. Teeth poor, partly carious, the crowns much worn away, transverse folds on the forehead, skin in the supraclavicular fossæ shows slight pad-like thickening, elastic; also the skin on the backs of the hands and feet is more elastic, otherwise skin on trunk is rather rich in fat. Several lens-shaped specks of pigment on the mucous membrane of the cheeks. Many places, on the skin more strongly pigmented, as in the folds of the palm of the hand, also in the vicinity of the nipples, on the backs of the hands, forearms, also about the waist. Breasts not enlarged. Mons Veneris rather rich in fat; no especial deposition of fat on hips. Findings as to cranial nerves entirely normal, except that *Chvostek II* distinctly positive. *Trousseau* negative. Pupils react promptly. Eye-grounds normal. Patellar reflexes weak. Size of heart normal to percussion; faint, weak, systolic murmur at *Erb's* point. Pulse 68, tension slight, blood-pressure (*Riva Rocci*), 65, liver not enlarged, spleen not distinctly palpable, neighborhood of the kidneys on each side not especially sensitive to pressure. Penis small, about 7 cm. long. Skin on penis folded. Testicles on each side about the size of a bean, soft, epididymis also small, somewhat hardened. Scrotum small, soft. Examination per rectum shows that the prostate is very small. Examination of the blood: leucocytes 12,000, of which 51 per cent. are neutrophile and 5 per cent. eosinophiles. In the urine no sugar, traces of albumin. Slight dullness over the right apex, very few râles. Vesicular murmur somewhat weakened. Therapy: Thyroidin tablets 0.1 gm. t.i.d. After two and one-half months report by letter that the myxedematous manifestations have improved, but the deterioration in strength has progressed.

**Symptomatology.**—The cases described show a very noteworthy agreement with one another. It is therefore not difficult to delineate the clinical picture of the condition. All cases show in pronounced manner the symptoms of late eunuchoidism, an exact description of which I need not enter into here. This syndrome, however, constitutes only one, although one of the most emphatic expressions in the total picture of the disease. To it is added in all cases a most irresistibly progressive cachexia, and mostly also, as far as investigations have determined, a pronounced anemia. Hence it occurs that such patients in spite of the boyish beardlessness of face, do not, as in late eunuchoidism appear younger than they really are, for the most part they rather appear prematurely old, and in some cases even a senile appearance comes to the face. There never occurs the development of an adiposity of the type of the eunuchoids. For the most part there rather occurs an increasing emaciation, that is associated with a feeling of weakness and with chills, and which persists in spite of all attempts at feeding up. Then there occurs more or less pronounced puffiness of the skin of the face, especially of the cheeks, and of the skin of the backs of the hands and feet, in many cases quite pronounced myxedema, that partially but not entirely retrogresses on thyroidin medication. There usually are added to the falling out of the hair on the face, trunk and extremities, thinning out of the hair of the head, eventually falling out of the hairs in spots, such as is seen in true myxedema, also thinning out of the eyebrows, eyelashes, and symptoms that also do not belong to true late eunuchoidism. Also brittleness of the nails was observed in my case. Also the loosening of the teeth and especially the marked wearing down of the crowns, as I saw in my case, perhaps too belong to the clinical picture. In many cases are found in addition to the puffiness of the skin, pronounced atrophy of the rest of the skin, and marked dryness and exfoliation. There further develops in the majority of cases pigmentations of the skin, especially in places exposed to light or where the clothing presses, sometimes, too, distinct pigmentations of the mucous membrane as in Addison's disease; in other cases a pigmentation that is more brownish is noted. Almost in no case are absent asthenia that increases to high-grade prostration of strength, mental sluggishness and apathy, further a feeling of pressure in the head, forgetfulness, insomnia, and eventually transitory rheumatoid pains in the limbs. In addition there exists hypotonia. The sugar content of the blood has not as yet been investigated. In cases in which the blood has been examined have been found in addition to the anemia, slight leucocytosis with mononucleosis and eosinophilia. Temporary polyuria has been reported remarkably frequently (*Rumpel*, *Gandy*, *Gougerot* and *Gy*). Occasionally also occur tetanic convulsions (*Claude* and *Gougerot*) or at least the symptoms of a latent tetany.

The relation of the numerous symptoms to the diseases of the individual ductless glands often meets, as will be understood, with difficulties. It seems to me that the simplest to explain is that syndrome that we learned to know in the exposition of late eunuchoidism, and that comes about through the degeneration of the sexual glands. It should only be mentioned in addition that in the cases that affect women, the retrogression of the genital apparatus and of the secondary sexual characters are present in a pronounced manner. At all events we cannot in the cases with pronounced retrogression of the genital apparatus, and especially the hair of the mustache, exclude the possibility that a degeneration of the suprarenal cortex does not play a rôle. In male individuals, it appears to me only necessary to assume such an involvement of the suprarenal cortex in the crassest cases, as in traumatic late eunuchoidism, in which the etiological factor is quite clear, quite severe manifestations of retrogression may occur. In women, however, there may perhaps be ascribed to the suprarenal cortex a greater significance in this direction, as we see after castration very slightly pronounced the ordinary retrogression of such secondary sexual characters as the hairiness of the axillæ and of the genitalia.

The changes in the hair of the head are to be referred to a degeneration of the thyroid gland, as are also trophic disturbances of the nails, probably also of the teeth, and further the apathy, headache, forgetfulness, etc., finally the myxedema of the skin. At all events it seems to me questionable whether the myxedematoid consistence of the skin is always of purely thyrogenic origin, as thyroidin medication very often does not fully control it. Such myxedematoid alteration of the skin is found not infrequently in the hypophysial dystrophia adiposo-genitalis; further such alterations occur not rarely if cachexia develops in Basedow's disease. I refer to the chapter dealing with this subject, and would like only to express the conviction that in such cases the skin changes may be brought into relationship with a (even simultaneous) degeneration of the glandular hypophysis.

The sclerosis of the hypophysis may also very well play a part in the rapidly progressive cachexia. That there does not ensue a distinct development of hypophysial obesity is intelligible when we consider the general cachexia in multiple ductless glandular sclerosis. If individuals who are not yet fully developed were to become the subjects of this disease, the absence of the eunuchoidal tall height would also be intelligible, as the action of the insufficiency of the sexual glands on the development of the skeleton might be compensated by the insufficiency of the hypophysis. I would bring still another symptom into relation with the hypophysis—the transitory polyuria. As is known we find this symptom quite commonly in diseases of the hypophysis, or in pathological processes at the base of the skull. We may readily conceive that sclerosing processes that have become established in the anterior lobe of the hypophysis temporarily act as irritants on the posterior lobes or on the pars intermedia. From this standpoint it seems to me worthy of mention that two of the cases of late eunuchoidism reported in the tenth chapter, in which we found transitory polyuria, developed after an acute infectious disease or after lues. Here the polyuria may well be regarded as hypophysial.

Hypotonia, high-grade asthenia and the pigmentations serve as manifestations of absence or deficiency [Ausfall] on the part of the suprarenals or, much more, the suprarenal medulla. Finally the tetanic spasms that occur point to an involvement of the parathyroid glands in the disease process. Here perhaps it may be thought that the lowering of the thyroidal and suprarenal activities can antagonize the occurrence of distinct tetanic symptoms even where there is high insufficiency of the parathyroid glands. I know that much that is hypothetical is bound up with these attempts at explanation. In one point, however, I believe I can scarcely err, namely, in the supposition that the rapidly progressing cachexia that is observed so frequently finds its explanation not in the functional disturbance of *one* ductless gland, but in the progressive degeneration of the ductless glandular system.

The *etiology* of multiple ductless glandular sclerosis of the ductless glands seems to be of diverse nature. In many of the cases acute infectious diseases have preceded the beginning of the disease. Thus in the case of *Josserand,* influenza; in the case of *Gougerot* and *Gy* a "hard to define acute" illness occurred, as in my case also. The case of *Sainton* and *Rathery* was syphilitic. In the case of *Claude* and *Gougerot,* and in that of *Brissaud* and *Bauer* there existed at the same time tuberculosis. Histologically, in the cases in which there were autopsies, there was found a simple sclerosis; except in the case of *Claude* and *Gougerot* where there was found in addition tubercle in the thyroid gland. It is indeed very likely that the ductless glandular sclerosis may depend very often on a tuberculous foundation, as *Poncet* and *Leriche* mention, although I cannot follow the connection of ideas of these authors

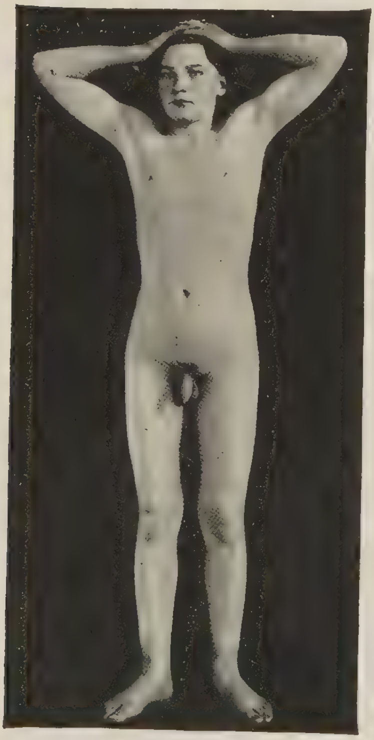

FIG. 77.—Case with insufficiency of several ductless glands (Observation LIV).

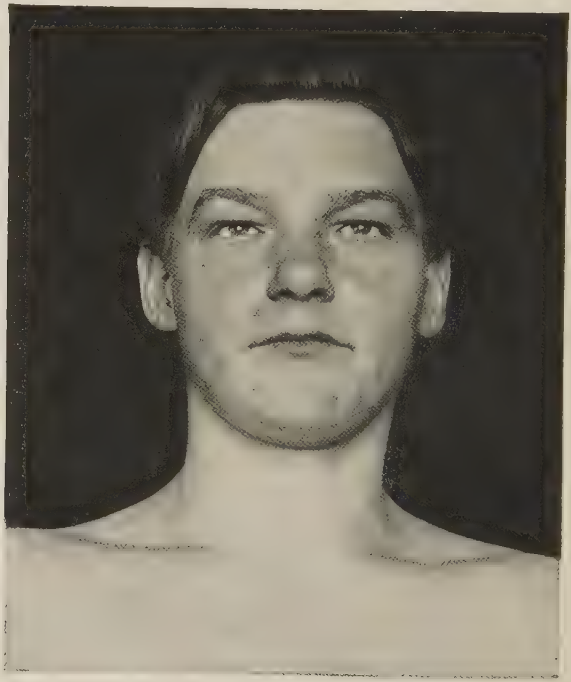

FIG. 78.—Slightly myxedematous facial expression.

when they ascribe to cases of dystrophia adiposo-genitalis, yes even to cases of acromegaly, a tuberculosis foundation.

In many cases the disease picture of multiple ductless glandular sclerosis develops quite spontaneously, without there being a preceding or an accompanying disease as the point of departure for the etiology. The opinion of *Claude* and *Gougerot* that there exists in such cases a congenital weakness of the ductless glandular system, so that a not well-definable deleterious agent brings this to degeneration, is not improbable. In such cases the organism, especially that which is still in a state of development, may come to a temporary manifestation of insufficiency on the part of the ductless glandular system.

I would regard the following as such a case:

*Observation LIV.*—J. K., seventeen years old (first medical clinic). One year ago typical tetany, two months ago typical epileptic attacks for the first time. Now tetany again. Of medium height, pale color of face, skin somewhat dry and exfoliative. Face distinctly myxedematous, especially the eyelids. On the backs of the hands slight myxedematous swellings. Hairs of the beard and axillæ are entirely absent, as is also the hairiness of the linea alba and the calves. Scanty hairs at the root of the penis. The testicles are very small and soft. As yet no libido, never erections nor pollutions. Finger nails very compact, strongly curved and ridged longitudinally. Teeth throughout strikingly small and poorly developed, terrace-like striations on the enamel (whether he had tetany in childhood cannot be elicited). Ossification normal. Blood-pressure 65. On the administration of even 200 gm. dextrose, no glycosuria. Neutrophile cells 54 per cent. Typical tetanic attacks. Slight apathy; on thyroidin medication the myxedematous symptoms disappear entirely, the blood-pressure soon rises to normal, the blood picture becomes normal.

After a year the case was examined by *Redlich.* There were new attacks of tetany, also epilepsy. There was nothing to be seen of the myxedematoid symptoms, and the secondary sexual characters had for the greater part developed, and the sexual life had begun to assert itself.

Thus in this case there existed, in addition to typical tetany and epilepsy, a simultaneous disturbance of the function of the thyroid gland and of the sexual glands. Perhaps the suprarenals (pronounced hypotonia) were also involved. Probably it was that the inhibition of development of the sexual glands was not occasioned directly by the disease of the thyroid. For this speaks the fact that thyroid-gland therapy immediately brought the manifestations of hypothyroidism to disappearance, while the insufficiency of the sexual glands gradually disappeared spontaneously.

*Claude* and *Gougerot* believe that also alcoholism may furnish an etiological factor. In this respect two cases of general *hemochromatosis,* concerning which *Falk* has reported, are of interest. As is known, there are found in such cases pronounced sclerosis of the liver and mostly also of the pancreas. In both the cases, as I myself had occasion to observe, there was also a premature diminution or cessation of the genital function, without the history furnishing a basis for a preceding disease of the genitalia. In both cases there was found also an almost complete falling-out of hair on the trunk and the extremities, and also that in the axillæ and on the pubis. The histological examination of an excised piece of skin showed, in addition to collections of pigmentation, abundant connective-tissue proliferation of the cutis, and in places also the sweat-glands and the hair follicles were replaced by connective-tissue strands. *Falk* believed that this sclerosis was also the cause of the falling-out of the hair. I incline more to the supposition that the involvement of the sexual glands in the general sclerosis had led to a retrogression of the secondary sexual characters.

For this assumption I find support in the investigations of *Weichselbaum* and *Kyrle*. In individuals, who do not as yet stand under the influence of the senium, *Weichselbaum* and *Kyrle* found on account of alcoholism cirrhotic alterations of the testicles, affecting interstitial cells as well as the glands of generation.

In the broad field of multiple ductless glandular sclerosis belongs perhaps a disease that *v. Noorden* has described as *degeneratio genito-sclerodermica*. It affects young previously healthy girls in whom the periods suddenly cease at the termination of an acute infectious disease after a previously normal development; marked emaciation and loss of appetite occur, a premature senility occurs, and there develop trophic disturbances of the skin; and in some cases in which the condition was looked for, the corpus of the uterus was found to be atrophic.

Further I would mention for consideration whether such a multiple ductless glandular sclerosis does not exist in many cases of *pedatrophy*. *Thompson* has described a noteworthy case in which sclerotic processes were found in all the ductless glands.

Finally I might here mention an apparently rather typical disease picture of which *Sir Jonathan Hutchinson*, *Hastings Gilford* and recently *Variot* and *Pironneau* have furnished examples. *Hastings Gilford* designates these cases as "*progeria*," *Gariot* and *Pironneau* as "*nanisim type senile*." As we shall see directly much speaks against our classifying, without other consideration, these cases with multiple ductless glandular sclerosis. I would say here, however, that at least an indirect connection with the ductless glandular system is here possible, and that the inclusion of the condition at another place appears to me less to the purpose.

I will here shortly report the three cases described up to the present. In the case of *Hastings Gilford* the observation extended between the fourteenth and eighteenth years of life of the individual affected. A photograph of the individual taken at the second year of life shows that the hair of the head was markedly thinned out already at that time; at the later investigations the patient showed a marked remaining behind in growth and in entire development. At fourteen years of age the boy was 113 cm. tall, weighed 16 kg. He was extremely thin, so that the cartilages of the nose and the veins and the tendons of the entire body were very prominent. The head was rather large, the facial skeleton relatively small. There were on the head only a few thin hairs, the eyebrows and the lashes were absent, almost completely, as were also the hairs of the trunk. The lower jaw was ill-developed, and there was especially a poor development of the clavicles. The musculature was poorly developed, the genitalia were about one or two years behind in their development, the skin was thin and dry, the nails were short and the anterior fontanelle had not as yet closed, and certain of the temporary teeth were still present. There was a falsetto voice; the intelligence was rather well developed. The individual made quite a senile impression. At the age of eighteen, the boy died with symptoms that gave thought to the diagnosis of "thymic or cardiac asthma." At autopsy was found an enlarged thymus gland and atheromatous alteration of the mitral and aortic valves; the coronary arteries were highly sclerotic. The capsule of the spleen was thickened, the kidneys were fibrous, the walls of the intestines and stomach were so atrophied that they were almost transparent. The liver was relatively large, the brain normal. The long tubular bones were rather slender, but the ends much thickened. Especially the condyles of the femurs and the arterial ends of the clavicles were swollen up. Ossification had been premature. Microscopically the ductless glands (thyroid, hypophysis, testicles and suprarenals) were apparently normal, there was no microscopical examination.

*Hutchinson* observed a three-and-a-half-year-old boy with the same disease. *Hastings Gilford* saw this case when it was fifteen years of age and followed it to its death two years later. There existed extreme emaciation, so that the bones and the tendons were very prominent. The abdomen was large, the condyles of the tubular bones were rather thickened, especially the distal epiphyses of the femurs, so that the patellas were pushed forward. The fingers were short, the size of the hands corresponding to that of a three-year-old child. The ossification represented that of a twenty-year-old youth. There were symptoms of a mitral and aortic failure, and death occurred with symptoms of a cardiac syncope. There was no autopsy.

The case of *Variot* and *Pironneau* was that of a fifteen-year-old girl. She weighed only 11.65 kg.—like a two-year-old child, was 102 cm. in height, size and dimensions corresponding with those of a five-year-old child. The appearance was entirely senile. Apart from isolated hairs on the head, the hair was entirely absent, even the hairs of the eyebrows and lashes. The skin was thin and folded, the panninculus adiposus was entirely absent. The muscles were relatively well developed, and stood up prominently through the thin skin. The nails were very small, the tooth formation was very bad, and second dentition was just appearing. Many teeth have fallen out without especial pain. The development of the genitalia had remained behind, and breasts especially had not developed. The intelligence was rather good. Up to the fifteenth month development had been entirely normal, and from this time it had remained behind. X-ray examination showed that the lower jaw was very atrophic and that the epiphysial junctures had for the most part closed. *Gilford Hastings* reports also a case of *Ransom* that possibly belongs here. It was concerned with a twenty-seven-year-old girl who was 135 cm. tall and weighed 16 kg. The father had been a heavy alcoholic. The girl's intelligence was feebly developed. Diarrhea had existed from youth, and later there had been a diabetes. The genitalia in their development represented those of a ten-year-old girl. The ovaries were absent. The girl was markedly emaciated and looked pronouncedly senile. At autopsy there were found fibrous changes in the spleen, lymph glands, the pancreas, kidneys, suprarenals, thyroid, hypophysis, etc. The heart weighed 6 oz. (about 176 gm.) and there were atheromatous changes in the aortic and mitral valves and in the aorta.

The cases cited show the greatest similarity to one another. Already *Hastings Gilford* remarked that his case and that of *Hutchinson* were so similar that the father of the first when shown the photograph of the second believed momentarily that it was that of his child. Also the case of *Variot* and *Pironneau* was similar to the first two, as is seen in the photographs these authors publish; it is also remarked by them, although their case is that of a girl. In all cases the disturbance in development began in the earliest youth. In all the inhibition of growth was very considerable, so that we could really speak of dwarfism. In all there was extreme emaciation, with the skin thin folded. In all were the muscles rather prominent. The osseous system showed the characteristic alterations. The dimensions remained childlike. The lower jaw was rather poorly developed, apparently also the upper jaw, causing perhaps the aquiline nose observed in all. The long bones were relatively slender, the ends of the bones thickened, the closure of the epiphyses was rather premature. The genitalia remained backward in development in all cases; and finally the absence of hair is common to all, affecting not only the hairiness belonging to the so-called secondary sexual characters, that on the lip, chin, axillæ, pubis, and trunk, but also the hair on the head, lashes, and eyebrows. This increased the senile appearance, which in all these cases is of high degree.

That here we are dealing with a morbid entity can in all likelihood be assumed from the similarity of the cases and the course of the disease. On the contrary the pathogenesis of this condition and the rôle of the ductless glandular system in the same seem to me to be as yet but little clear. *Variot* and *Pironneau* point out that in the case of *Hastings Gilford* the suprarenal showed fibrous degeneration, and see in the disease picture the sequel of a suprarenal insufficiency's setting-in in youth. *Apert* goes still further and sees the cause in a damaging of the suprarenal cortex. In the coming on of the characteristic disturbances in the hairiness and in the genital sphere he sees in this disease a countertype to that of tumors of the suprarenal cortex. *Hastings Gilford* believes on the contrary that we are to ascribe to the hypophysis a "growth center" of considerable importance. The results of the one autopsy done on these cases up to the present are insufficient, as there was no microscopical examination of the ductless glands. It was mentioned only that the suprarenals were sclerosed. In the case of *Ransom*, that does not belong with certainty to this group, the other ductless glands were also apparently sclerosed. If now also the microscopical examination in such cases would also furnish an extensive sclerosis of the several ductless glands, it would not necessarily be shown the disease of the ductless glands was *primary;* it would also be possible that we might be dealing with a diffuse sclerotic process involving the entire body, that has also involved the ductless glandular system, such a general process as we regarded above as possible for hemochromatosis and which is perhaps also true for pedatrophy.

Then we would be dealing with a *secondary* sclerosis of the ductless glandular system, that at all events lends to progeria many of the striking features of ductless glandular sclerosis, and which may play the chief rôle in the enormous cachexia and the senilism of these individuals.

In the clinical picture of progeria are some features that seem to me hardly compatible with the assumption of a ductless glandular sclerosis. In the three typical cases the intelligence was fairly well developed, which rules out a strong involvement of the thyroid gland. Especially, however, does it seem to me that the premature ossification points to a sclerosing process independent of the ductless glandular system, as otherwise we would expect considerable retardation of ossification. The severe disturbance in the development, or the retrogression of the hair, can indeed very well be brought into relation with an involvement of the suprarenal cortex; it is, however, conceivable that it has its foundation in a severe atrophy of the skin. It was already in the first chapter pointed out that we must not regard old age, as *Lorand* does, simply as a gradual degeneration of the ductless glandular system; but consider that the ductless glandular system, like the rest of the organs takes part in a general involution of old age It seems to me that the same thought can be applied also to premature and childish senility.

**Differential Diagnosis of Multiple Ductless Glandular Sclerosis.**—The cases out of the literature that I have quoted show a remarkable agreement with each other, so that for the most part the diagnosis does not meet with difficulty, especially so in that the retrograde processes in the genitalia and the secondary sexual characters constitute especially striking symptoms. The delimitation from pure late eunuchoidism may indeed become difficult. Marked puffiness of the skin, thinning of the hair of the head in patches, and of the hair of the lashes and eyebrows, speak against late pure eunuchoidism, as do also marked emaciation and cachexia. For the delimitation from pure myxedema I regard as important the partial or extremely deficient results attending thyroid gland therapy. Concerning the diagnosis from pure Addison's disease nothing further need be said. As far as diagnosing it from hypophysial dystrophia adiposo-genitalis is concerned, it is not known to me that in this disease such a high-grade atrophy of the genitalia of adults occurs, as was described under late eunuchoidism; naturally the absence of symptoms of brain tumor is also important, although it must be remembered that in the case of *Sainton* and *Rathery* there was found at the same time a malignant cystic degenerated tumor of the hypophysis. Therefore it seems that a combination of multiple ductless glandular sclerosis and hypophysis tumor may occur.

Up to the present the *treatment* has been of little avail. In the cases of *Rumpel* and of *Djeinil Pascha* the use of thyroid gland was negative, and in *Gouilloud's* case doubtful. French authors have tried a combined ductless gland therapy (thyroidin, hypophysis substance, sexual gland substance, and suprarenal substance) and have sometimes seen temporary improvement of individual symptoms under the influence of these, yet the progressive cachexia can for the most part not be essentially influenced.

## Gigantism

**Historical.**—It can be readily understood that gigantism usurped the interest of the laity and physician from early times. Indeed a philanthropist even founded a prize in order that by the intermarriage of giants a larger and stronger race would be produced. For the first valuable scientific observations concerning this interesting phenomenon we are indebted to *C. v. Langer*. *v. Langer* distinguished between normal and pathological giants. He described three skeletons of normal giants, one from the Berlin Pathological Institute, one from Hunterian Museum, and one from Trinity College, Dublin. These giants enjoyed good health until a high age; they showed in general normal dimensions of their skeletons corresponding to their size, therefore rather large skull and a relatively large upper body, the upper length somewhat exceeding the lower length. In the other group, the pathological giants, *v. Langer* first pointed out that here certain pathological alterations of the skeletons were present, such as relatively small cranium with enlarged sella turcica and enlargement of the facial skeleton with enormous lower jaws, widening of the pneumatic spaces, increased development of the insertions of the muscles, certain abnormalities of the pelvic girdle, frequency of genu valgum, in short a series of alterations that to-day we would designate as acromegalic. *v. Langer* pointed out that from illustrations also degeneration of the soft parts, such as enlargements of the tongue and the lips, had existed.

Then *Sternberg* in a detailed work pointed out the frequency of the combination of acromegaly and gigantism According to *Sternberg* about 40 per cent. of all giants are acromegalics, and about 20 per cent. of all acromegalics giants. This question entered upon a new stage when especially the French school sought to define the relation between acromegaly and gigantism. After *Massalongo* had designated acromegaly as late gigantism, *Brissaud* and *Meige* came forward with the teaching that acromegaly and gigantism are one and the same disease and depend on the same cause, namely, an alteration of function of the hypophysis, which leads in youthful individuals to gigantism, and in older individuals, those in whom the epiphysial junctures have already ossified, to acromegaly. These authors also support the view that only the acromegalic giants should be termed proper giants, and that gigantism should always be regarded as the disease. This opinion, which was actively contradicted by *Pierre Marie*, *Launois* and *Roy* have tried to support in several researches and in their monograph. Both these authors show, in convincing fashion, that the greater part of the giants thus far observed have been acromegalics, or have later become acromegalic. Also

*Biedl* has considered the subject of gigantism wholly in his chapter on the hypophysis.

## Symptomatology and Types of Gigantism

According to the opinions thus far existing in the literature, as to the pathology of gigantism, it is not possible to define it uniformly. The difficulty begins already with the question as to which individuals should be regarded as giants. *Bollinger* proposed regarding as tall, human beings whose height reached 205 cm., and only speaking of giants when the height exceeded 205 cm. This classification is naturally quite arbitrary. According to it a whole group of the cases reported in the literature would no longer be regarded as belonging to giants. Just as arbitrary seems to me the opinion occurring in the French literature that only those giants that bear acromegalic features should be regarded as true giants. Even though well-proportioned, nonacromegalic giants are apparently among the greatest rarities, yet, according to the definite statements of *v. Langer* and *Virchow*, their existence is not to be doubted. Therefore it seems to me to the point to adhere to the old classification of *Langer* and to distinguish between *normal* and *pathological giants*. Moreover we find described in the literature a group of cases, whose height lay between 190 and 200 cm.; cases that showed no acromegalic features, but on the other hand, all the signs of typical eunuchoidism. Here, therefore, there lies before us all the signs of a *potentized form of eunuchoid tallness*, and for this the designation eunuchoid gigantism seems to me not without foundation. The cases coincide in part with those cases which *Launois* and *Roy* have called infantile gigantism. Considering the fact that I have sharply separated eunuchoidism from infantilism—I shall come back to this differentiation in the next chapter--I must regard the designation eunuchoid as more precise than infantile. I would here point out that a portion of the giants described by *Launois* and *Roy* as infantile are not pure eunuchoids, but already bear the acromegalic features. Finally, as to what concerns the *acromegalic giants* I shall take pains to show that here there are very diverse types, those types in which from the beginning acromegalic manifestations are distinctly prominent; those types which to use an expression of *Launois* and *Roy* "acromegalize" only later; those types which possess the eunuchoid features or even pronounced eunuchoidism from youth on; those types to whom a kind of late eunuchoidism comes only later, and finally those types in whom the eunuchoid features are entirely absent, in whom, moreover, the function of the sexual glands and genitalia are entirely normal, or even perhaps temporarily abnormally increased.

In the great multiplicity of the manifestations of gigantism a uniform exposition of the symptomatology is scarcely possible; it seems to me more to the purpose to adduce examples of the various types from the literature, whereby I would mention that all possible transitions between the groups occur.

I will not enter further into the subject of normal giants. In the historical introduction I have already mentioned the most important facts.

Of the eunuchoid giants I mention the twenty-seven-year-old man described by *Launois* and *Roy*. (Soc. de Biol. 10 Jan., v., 1903.) In this individual the increased growth in height apparently began after an attack of typhoid fever.

I shall now adduce a series of cases relating to acromegalic giants, in whom the function of the sexual glands was normal. As the first example I communicate a case that I myself had occasion to investigate.

*Observation LV.*—B. O., "Bulgarian giant," born in Gross-Wenkheim near Bad Kissingen, thirty-seven years old. The male members of the family are almost all rather tall. The tallest was his father's brother, who measured 186 cm. His father measures 180 cm. B. O. states that he first began to exceed his school companions in growth at the seventh year of life. At twelve years of age he measured about 206 cm., and at twenty-four years of age had attained his full height (212.5 cm.). He served in the "Bayerischer Leibregiment" and was at that time examined by the chief physician, *Dr. Seggel*. At that time he was entirely well, and had grown completely used to the military service. He says that as a young man he weighed 145 kg. Especially in his eighteenth to nineteenth years had his appetite become enormous. He says that it was easy for him to devour at one meal 1 kg. of meat with copious additional fare. The highest weight was 195 kg. He had never suffered from headache. According to his statement the sexual development was entirely normal. In 1900 he married a woman who was 187 cm. tall. After one year she bore an entirely normally-carried child, who died after four weeks. Then later the woman had two premature deliveries, about in the fifth month. The potency up to this time had, according to his statement, not diminished. Six years ago he suffered from influenza and since that time "has had to do with a cough." The apex of the right lung is defective.

The man now measures 210 cm. as a distinct kyphosis exists, it is very probable that his statement that he formerly measured 212.5 cm. is perfectly correct. The span width reaches 220 cm., the breadth of the shoulders 52 cm., the circumference of the chest 118 cm., of the waist 100 cm. Distance from the anterior superior iliac spine to the floor 124 cm.

There exists, as already mentioned, distinct kyphosis, the enormous shoulder blades project prominently. The clavicles are enormously developed. The circumference of the upper arm measures 29 cm., formerly when the patient was very muscular it reached 68 (?) cm.

The distance of the external malleolus of the wrist-joint to the point of the middle finger is 27 cm.

The greatest circumference of the hand is 30.5 cm. The greatest circumference over the metacarpopharyngeal joint is 27 cm.

The middle finger, from the metacarpopharyngeal joint to the point of the finger is 14 cm., the circumference of the thumb 9 cm.

Distance between the anterior superior spine and the upper border of the patella is 57 cm.; length of foot 33.5 cm. Circumference around the ankle-joint and heel 43 cm.; length of great toe 9.5 cm.; circumference of the same 11 cm. The head is enormous. The fronto-occipital circumference reaches 67 cm. The occipitomental circumference 73

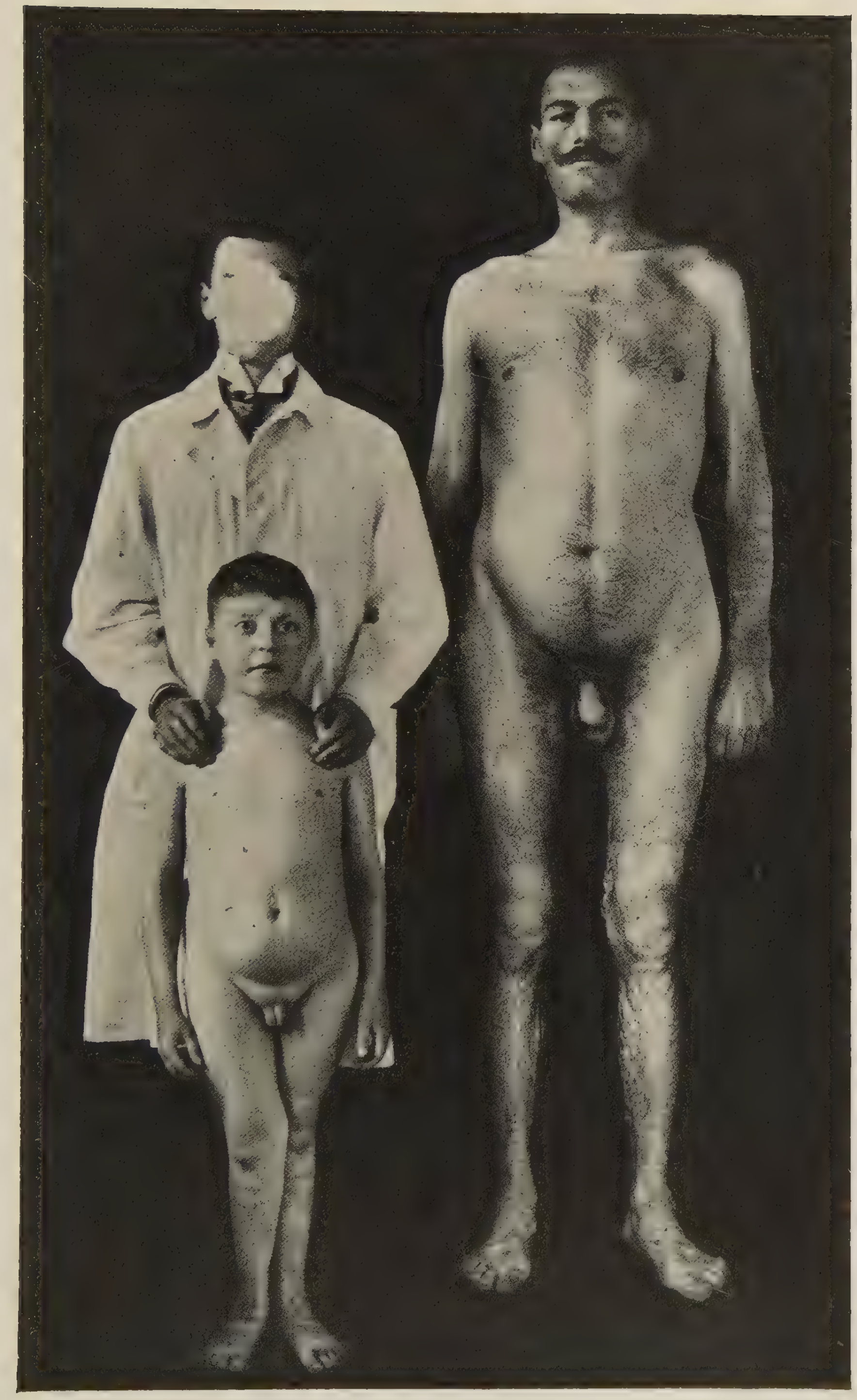

FIG. 79—Gigantism (Observation LV) and hypophysial dwarf (Observation XLIV). The normal individual measures 183 cm.

cm. The superciliary arches project markedly, as do also the malar bones. There exists distinct prognathia. The anterior upper incisors are 1.5 cm. from each other. The set of teeth is normal; only one tooth is absent. The tongue is disproportionately large. The palate is in proportion. The least circumference of the neck is 42 cm. The pomum Adami projects markedly. The thyroid gland is palpable and is in proportion. The voice is very deep and low. The hairiness is very abundant. The mustache is well developed, the man must shave every two days. The chest and the linea alba are extensively provided with hair. Also the hairiness on the genitals, the perineum and in the axillæ is abundant. The genitalia are proportioned to the other relations. Heart dullness: upper border of the fifth rib, left sternal border, 7–½ cm. to the left of the border of the sternum. Heart sounds clear. Slight tachycardia(105).

The orthodiagram shows a greatest heart breadth of 13 cm., breadth of the aortic shadow 7 cm. These measurements are relatively very small. Tuberculous affection of both apices. The stomach is enormously large, sac-like, reaches 20 cm. below the navel. The ordinary bismuth meal is just enough to fill the fundus of the stomach.

Blood examination: Hemoglobin (according to *Sahli*), 80 per cent.
Erythocytes, 5,720,000
Leucocytes, 5600, of which:
Neutrophilic polymorphonuclear, 65 per cent.
Lymphocytes, 20 per cent.
Large mononuclears, 9 per cent.
Eosinophiles, 6 per cent.

The examination of the urine shows sugar 0, albumin 0, urobilin 0, indican+

Eye examination (*Dr. Ulbrich*). The pupillary distance is 72 mm. (normal about 65 mm.) The length of the palpebral fissures 33 mm. (normal 28 mm.).

On the contrary we find that globes lie abnormally free on all sides and that the width of the cornea is not greater than the normal average (11 mm.) Eye-grounds normal. Visual field and color field normal.

The X-ray plate of the hand shows entirely normal ossification. The enlargement affects bones and soft parts rather to a like degree.

The X-ray plate of the head shows enormous relations. We see the frontal and the maxillary sinuses considerably broadened and, further, the distinct prognathia of the lower jaw. The bones of the cranial vault are enormously thickened, the sutures markedly projecting, especially striking is the enormous external occipital protuberance.

The sella is markedly enlarged and deepened; the posterior clinoid processes are distinct, and the anterior less evident. The introitus of the sella is relatively not very wide (Fig. 80).

We are hence dealing in this case with a typical acromegalic giant. The acromegalic tendency became evident at a rather early age and seems to have progressed very gradually. At least this man can give no sure statement as to when the coarsening of the features and the prognathia began to develop. He states that his hands and feet have not become essentially larger in the last ten years. We have better data so far as the kyphosis is concerned. During the military service, hence fourteen years ago, this did not exist. Another point is furnished by the diminution of muscular strength, which at about the twentieth year must have been enormous. The pulmonary tuberculosis that has developed in the last year can surely be

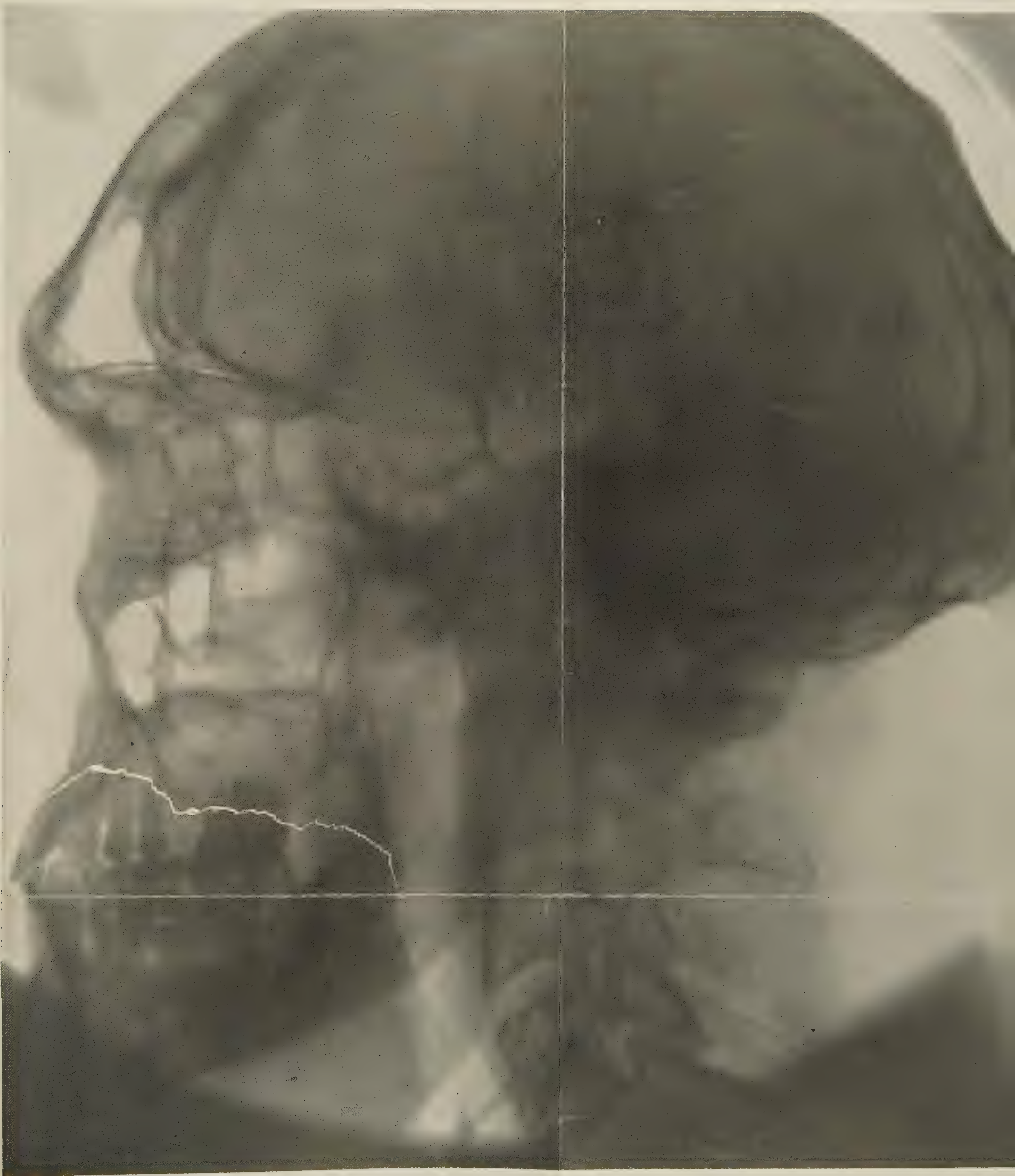

FIG. 80.—Skull of a giant (Observation LV).

held responsible for only a small portion of the decay. Signs of increased intracranial pressure are not as yet present in this patient; with which the X-ray findings—that show especially a deepening of the floor of the sella, are in accord. Especially important in this case is the behavior of the sexual glands. The functions of the genitalia up to the present time have been entirely normal. At all events up to his thirtieth year the patient was capable of reproduction. At most we could say that the early death of the first child and the two following premature deliveries on the part of his wife point to a diminished valuation of the semen, but this assumption does not seem to me to be well considered. In agreement with the sexual potency we find the dimensions of the skeleton normal, and the hairiness even abnormally strongly developed.

Also the giant of *Huchard* and *Launois* had two children. In this case the abnormal increase in growth began in the twelfth year of life. At the age of eighteen he was 197 cm. tall. The genitalia were entirely normally developed. He attained the age of sixty years and at that time showed typical acromegalic manifestations. The sella turcica was the size of a nut. Sclerosis of the anterior lobe was found at autopsy. This case has been brought forward as a demonstration against the hyperfunction theory of acromegaly. Incorrectly indeed, as we may well imagine that in late life the acromegalic manifestations must not necessarily retrogress when there occurs without anything else a secondary sclerosis of the hypophysis.

The case of *Buday* and *Jancso* showed an abnormal increase of the potency that was at all events short in duration. At seventeen years of age this patient was very potent, and performed coitus four to six times every night. From the twentieth year on he gradually became impotent. It is noteworthy that this case was only 103 cm. tall when he was twenty years old. Now he first began to grow appreciably and at the age of thirty-five years had attained the height of 198 cm. He now showed distinct acromegalic symptoms; there was found a large tumor of the hypophysis, the genitalia were atrophied, the length of the lower part of the body was very considerable, there existed a genu valgum, the epiphysial junctures were ossified (the abnormal growth has ceased for two years). In this case we have the sort of late eunuchoidism combined with acromegaly. It is very noticeable that in spite of the increased sexual function, the epiphysial junctures remained open between the seventeenth and twentieth years.

I would regard the case described by *Cushing* as one in which the late eunuchoidism began later. This thirty-five-year-old patient came from a healthy family. The father was six feet tall. At the age of thirteen years the patient first began to grow enormously rapidly; at the age of nineteen years he was 6 ft. 4 in. tall, weighed 200 lb. and was of extraordinary strength and he was intelligent, a good student, and "aside from an uncontrolled libido sexualis" had good manners. Especially noteworthy seems to me the fact that only latterly did the obesity that occurred assume the eunuchoid type (as far as I can see from the pictures). This is true also of the absence of beard, and the eunuchoid hairiness. "He has practically no beard, and except for a scant pubic growth of feminine distribution, the skin of the trunk and extremities is practically hairless." The hair of the head was abundant.

Also in the case described by *Levi* and *Franchini* did there occur a late eunuchoid obesity.

The abnormal growth began in this person, who was sixty-five years old, at the age of eight to ten years, the secondary sexual characters were apparently normally developed at the time of puberty, there were few erections, however, and there never had existed an especial libido. The external genitalia were normal, as was also the mental development. He was always weak muscularly, in the last few years obesity developed, the distal parts of the extremities showed a considerable enlargement, there existed cervicodorsal kyphosis, in short the signs of an acromegaly that had gradually developed over a long period of time. The epiphysial junctures were closed.

I now adduce several examples of the eunuchoid type, in which the symptoms of deficiency on the part of the sexual glands already exerted an influence on skeletal formation in early youth Here belongs the giant Charles described by *Launois* and *Roy*. In the thirtieth year of his life, his height was 204 cm. The lower length was considerably more than the upper length. The penis was small, the testicles were very small, and the prostate also was small. He had had on several occasions erections, but never ejaculations. The hairiness of the trunk was typically eunuchoid. The epiphysial junctures were entirely open. In later life, acromegalic features made their appearance.

A pronounced case is reported by *Cushing* that on account of the monstrosity present I shall herewith adduce: thirty-six-year old man; he was already as a boy abnormally tall, and from the fifteenth year on grew enormously. For ten years he has been sick and weak. At autopsy the body measured 251.5 cm., the skin is delicate, hairness of the head good, no growth of beard, no axillary hairiness, sparse hairiness of the pubic region. The genitalia are small, the testicles atrophied. The distal epiphysial juncture of the radius is still open, no alimentary glycosuria. Distinct symptoms of acromegaly are present. The sella turcica is very much enlarged (2.2 to 2.7 cm.) and the hypophysis consists, in great part, of a cyst.

Also in such eunuchoid giants may the acromegalic alterations be very significant. There are also known female eunuchoid giants As example I adduced Lady Aama, described by *Woods Hutchinson*. She was about seventeen to nineteen years old, 244 cm. tall, and the lower length far exceeded the upper length; hands and lower jaw were very large. The genitalia were infantile, the mons Veneris was poorly developed, the labia majora were flat, the clitoris was well developed and resembled a poorly-developed penis.

The ovary on each side was very small, and changed into glandular masses. The hypophysis was enlarged, the sella turcica was destroyed, the mammæ were entirely hypoplastic.

I believe that the examples I have furnished suffice to show the enormous multiplicity of the manifestations of the pathological forms of giant growth. The symptoms of eunuchoidism or late eunuchoidism are combined with those of acromegaly in the most diverse ways. If we disregard, however, the quite rare cases of pure eunuchoid gigantism, we find indeed that the manifestations of eunuchoidism and late eunuchoidism are very common while the manifestations of acromegaly are present almost always regularly, or that they develop later. In this connection the classification of pathological giants by *Launois* and *Roy* is very correct, even if it is not just to the uncommonly numerous types.

**Pathogenesis.**—If we now turn to a pathogenesis of gigantism, our first task will be to test whether the formula of *Brissaud-Meige*, that also has been adopted by *Launois* and *Roy*, is in the position to explain the manifold types of gigantism. *Brissaud* and *Meige* have expressed the opinion that gigantism is nothing other than an acromegaly beginning in early youth, that is, before the closure of the epiphyses. A great difference between acromegaly and pathological gigantism now exists, before everything else, in the behavior of the sexual glands. I must here again point out the fundamental difference in the relation of the glands of generation and the interstitial glands in typical acromegaly. The first shows temporary increase of their function, but then there very commonly occurs very premature disturbances or entire loss of their function while the function of the interstitial glands is rather more emphasized or at all events, apart from very rare cases, shows no disturbance in the course of the disease. In gigantism we see this behavior in but few cases. In the majority of cases the manifestations of eunuchoidism are prominent from the beginning, or later there occur manifestations of late eunuchoidism. We have now learned to know a similar behavior of the sexual glands in early acromegaly.

There we have described cases in which also the interstitial glands showed disturbances of their function. This allows them to be used in the sense of *Brissaud-Meige's* formula. There also we have learned about sure cases of acromegaly, that came to manifestations of acromegaly while the epiphysial junctures were still open. Increase of function of the hypophysis alone, hence, does not lead to gigantism. We must assume in addition to it a potential tendency to growth, that may be either proportionate (normal giants), or as it is mostly, disproportionate, partly through a preponderance of the function of the hypophysis, partly through an insufficiency of the interstitial glands and probably also through many other factors. While in acromegaly we certainly find a tendency to hyperfunction and hyperplasia of other ductless glands in which, however, always the increase in function of the hypophysis remains quite in the foreground, in gigantism the tendency to increase in function of the whole ductless glandular system seems to belong quite to the essence of the disease. It would seem that in addition to the hypophysis all the ductless glands are involved in a predominant manner in the hyperplasia—the suprarenal cortex, probably also the chromaffin tissue, etc. How enormous the pancreas may become is shown by the autopsies of the giants *Bassoe Peter* and of the *Tambourmajor*. The pancreas of the former weighed 275 gm., that of the latter 250 gm. Also the sexual glands may be involved in this hyperplasia. In addition to this tendency to hyperplasia there exists, however, a lability, a ready exhaustibility of the hyperplastic ductless glandular system; this seems to affect the most readily the sexual glands, in which degenerative processes may be established prematurely, indeed under circumstances the sexual glands (and especially the interstitial glands, that indeed differ from the other ductless glands in that they attain full maturity not until the time of puberty, may be disturbed in their development from the beginning. Also the development of the nervous system may suffer damage from this fact. The monstrous eunuchoid giants are the most deficient mentally. In addition to the sexual glands the other ductless glands mostly rapidly show signs of decay. The frequency of diabetes in youthful giants is known. In the great decrepitude and muscular weakness perhaps there is involved a degeneration of the chromaffin tissue Even in the hypophysis, such degenerative processes frequently occur, if the individuals attain a high enough age. I refer to the case of *Huchard* and *Launois* in which the hypophysis was found to be sclerotic, or to that of *Cushing* in which the hypophysis was in great part converted into a cyst. How rapidly the decay can enter in just these monstrous giants is shown by numerous cases in the literature. The enormous muscular power of which these individuals were wont to be so proud gives place in a few years to a great weakness. The ductless glandular system has exhausted itself and the organism fades rapidly like a plant driven to rapid growth by artificial means. Mostly the invalidism is rapidly made an end to by an intercurrent disease. *Woods Hutchinson* tells of eight giants that died on the average in their twenty-first year of life.

Investigations of the respiratory metabolism of giants, as well in the time of bloom as in that of decay, would be very important. I do not know of any of them. With regard to the other metabolism investigations, there are only the statements of *Levi* and *Franchini*, who in one case found increase of the elimination of amino-acids, ammonia, and neutral sulphur.

On the basis of what has been said above, I would assume in gigantism an abnormal mapping-out [Anlage] of the whole ductless glandular system, and would not, as have other authors, simply include it in the chapter on acromegaly. We know indeed that there are other forms of gigantism setting in in early life in which not the hypophysis, but other ductless glands (the epiphysis, the suprarenal cortex, the sexual glands) occupy the chief rôle in the pathogenesis In such cases there may indeed appear even simultaneous manifestations of hypophysial insufficiency (confer the case of *Raymond* and *Claude*). But as I mentioned already at the beginning the conception does not seem to me established as yet. I must leave open the question as to whether the hyperplastic mapping out of the entire ductless glandular system is only a partial phenomenon of an abnormal mapping out of the entire organism. We know indeed of a gigantism of individual extremity masses. I refer to the communications of *Fischer*, *Manasse*, *Wiedenmann*, *Grünfeld*, *et al.* We cannot hold the ductless glandular system responsible for such an abnormal growth tendency, even though there are found, also not rarely, certain anomalies of this system, *e.g.*, cryptorchidism on the same side.

## CHAPTER XII

# VEGETATIVE DISTURBANCES, NOT DIRECTLY DEPENDENT ON DISEASES OF THE DUCTLESS GLANDS

The words "vegetative disturbance" [Vegetationstörung] to my knowledge originated with *Kundrat.* By them we understand any inhibition of development. Since the time it was known that the growth, and especially the normal development of the organism was only guaranteed by a normal development of the ductless glandular system, modern investigation has been directed toward seeking the cause of the different vegetative disturbances in the ductless glandular system. In the foregoing chapters an entire series of vegetative disturbances were comprehended, which to-day we are justified in regarding as referable to a functional disturbance of individual ductless glands. It seems important for the following exposition, again briefly to sketch what these are:

1. Absence of the thyroid leads to dwarfism; in this is found characteristic disturbances of ossification, consisting in a high-grade remaining behind in development of the bone nuclei, and in the closure of the epiphyses, further in a disturbance in development of the bone marrow; what, however, has already been formed of the bones is of abnormal hardness; further there are found disturbances in the dentition, and in development of the central nervous system, whereby the development of the intelligence suffers. Further there are found the characteristic myxedematous alterations of the skin, and disturbances in the development of the genitalia.

2. The vegetative disturbance in endemic cretinism is not dependent only on the goitrous degeneration of the thyroid gland. Much more is it likely that the deleterious agent acts also directly on the central nervous system and on other ductless glands, for instance, the hypophysis. Thereby the vegetative disturbances are extremely manifold, the individuals remain very much behind in growth, but the disturbance in ossification is not disproportionate, one time the developmental disturbances of the central nervous system may stand in the foreground, another time the inhibition in growth, and another time perhaps the disturbances in the development of the hypophysis.

3. Pronounced inhibition of development is found also in diseases of the hypophysis that develop in early youth. In this case there occur, at least in a suggestive manner, eunuchoid dimensions on account of a developmental inhibition of the sexual glands that exists much in the foreground, and further there occurs eunuchoid distribution of fat. Disturbances in the development

of the bone nuclei and of the epiphysial junctures occur distinctly only in most severe cases. The intelligence develops normal, although these individuals show the characteristic temperamental attitude.

4. Also disturbances in the development of the suprarenal cortices perhaps also lead to definite vegetative disturbances; very little clearness as to this point exists, however.

5. Isolated disturbances in the development of the sexual glands leads to eunuchoidism with characteristic distribution of fat, characteristic dimensions of the skeletons, remaining open of the epiphysial junctures, especially those that close latest under normal conditions, and a characteristic psychic attitude with normal development of the intelligence.

There remains now a group of vegetative disturbances that of late have frequently been brought into association with the diseases of the ductless glands. In some of these the relation to the ductless glandular system is not yet sure, in others the disturbances on the part of the ductless glands constitute only one component of the clinical picture. Finally in others I would deny the connection. In this great group of vegetative disturbances I would include true infantilism, true dwarfism, chondrodystrophy, rachitic dwarfism, and Mongolism. In the exposition of each disease, its relation to the ductless glandular system will be especially considered. We shall not enter further into the subject of dwarfism in microcephalus and porencephalus. I have described dwarfism with hydrocephalus in the chapter on hypophysial dystrophy.

## I. INFANTILISM

**Historical.**—The first cases of human beings who for their life time remained in a childish stage of development [pathologically] were described by *Dancel* and *Baillarger*. The case of *Dancel* was that of a woman twenty-four years old who was 94 cm. tall and showed a mental and physical development of a four- to five-year-old child. *Lasegue* coined the name infantilism [-us] He understood by it a condition of persistence in the adult of the psychical and physical characteristics of a child. The first exact description was made by *Lorain*. He describes a form of infantilism that he describes as "Characterisée par la debilité, la gracilité et la petitesse du corps, par une sorte d'arrét de développement, qui porterait plutôt sur la masse de l'individu que sur un appareil spéciale: en un mot des subjets atteint d'une juvénilité persistente qui retarde indéfiniment chez eux l'establissement integral de la puberité." *Lorain* and his pupil *Faneau de la Cour* already stated that the different harmful influences that may affect the juvenile organism may lead to infantilism.

The question has been especially discussed in the French and Italian literature, ever since *Brissaud* set forth a form of infantilism that he referred to as insufficiency of the thyroid gland in child life. *Brissaud* considers that the type *Lorain* constitutes a dystrophic condition, and is brought about and maintained by a chronic congenital or inherited disease during the period of growth.

The views of *Brissaud* have been adopted in recent time by *Bauer*. *Bauer* regards only the type *Brissaud* as true infantilism and separates all other forms from the type *Brissaud* as "chétivisme." *Hertoghe* and *Ausset-Brêton* go still further than *Brissaud;* they see in all forms of infantilism an expression of a congenital damaging of the function of the thyroid gland and thus seek to establish all forms on a uniform basis.

*Ferranini* was the first to oppose this view. *Ferranini* again separates the two forms of infantilism, and regard the type *Lorain* as the sequel of a developmental deformity, and the type *Brissaud* as the sequel to the standstill of development. *Ferranini* sets forward the significance of the congenital or early inherited heart defect in the pathogenesis of infantilism (cardiodystrophic infantilism). *Carré*, and *Gilbert* and *Rathery* hold similar views. In recent time, especially *E. Levi* has opposed the views of *Brissaud*, in that he mentions that not all the true infantilisms are to be referred to an insufficiency of the thyroid gland. The type *Lorain* should also be regarded as true infantilism. Before this *Sante de Sanctis* had already again sharply separated the two types and emphasized the significance of various factors for the genesis of the type *Lorain*, factors such as hypoplasia of the vessels, chlorosis, disposition to tuberculosis, hereditary syphilis, malaria acquired in early youth, pellagra of the parents (*Agostini*), etc., *de Sanctis* further separated the true form of psychic infantilism from idiocy. He also was the first to attempt to explain the genesis of the type *Lorain* through alterations in the ductless glandular system. The delay in the physical and psychical development is never the result of isolated alteration of an individual ductless gland, but is produced by a "deviation de la fonction harmonique formative-protectrice de toute les glandes á secretion interne." In an interesting study, *R. Anton* has described the psychic side of infantilism. General infantilism was defined by *Anton* as "a developmental disturbance, that causes the entire organism to remain behind at the child type, but prevents the reproduction of the individual in the sense of his species. Thereby not only the physical earmarks, but often also the psychical characteristics of the child persist."

With general infantilism *Anton* includes:

A. The infantilism with myxedema and cretinism.
B. Mongolism.
C. Infantilism through absence or atrophy of the genitalia.
D. Infantilism with primary lesion of the visceral glands, especially the suprarenals, the thymus gland, and the pancreas.
E. Infantilismus dystrophicus, with the following etiological variation: Infantilism in vascular aplasia.

in primary brain lesion, unilateral or bilateral;
in hereditary syphilis;
in alcoholism or other poisonings (lead, mercury, etc.) of the parents;
in other diseases and metabolic disturbances that are acquired early, such as tuberculosis, chlorosis, and cardiac defects;
through deformities due to bad hygienic surroundings and to insufficient nourishing of the child.

Of partial infantilism, I mention especially the infantilism consisting in an atrophy of the genitalia, and the pure psychical infantilism.

I would finally especially emphasize here the excellent studies of *di Gasperos*. Here we find five cases described in detail, which, as we shall see later, are fine examples of true infantilism. Especially carefully also does *di Gasperos* handle the psychical side of the problem.

*Schüller* also divides infantilism into two forms: He distinguishes a dystrophic form conditioned by hereditary diseases, or diseases acquired in early youth, and a form whose pathogenesis is seen to depend on a lesion of a definite ductless gland (thyroid, hypophysis, etc.).

The regular remaining behind in the development of the genitals in the type described by *Lorain* has induced many authors to term "infantilism" the most various conditions in which the genitalia remain more or less hypoplastic. Thus we find in the literature numerous cases of true gigantism published under the title infantilism plus gigantism. Further we find published numerous cases of infantilism whose description would correspond to that which in a former chapter we have regarded as eunuchoids, or cases that at all events must be regarded as transition forms between eunuchoids and true infantiles. This is especially the case in the new expositions of the subject by *Peretz*, and by *Pende*. In the work of *Peretz* we find nearly all the ductless glandular diseases associated with developmental disturbances classified as infantilism. Even infantile features are ascribed to hypergenitalism. *Gandy* terms "infantilism reversif ou tardif" cases in which after completed development a retrogression of the genitalia and the secondary sexual characters begins (confer "late eunuchoidism," Chapter X). The ductless glandular theory has found an especially ardent advocate in *Pende*, who assumes as the cause of infantilism a disease of the ductless glandular system. He bluntly calls infantilism a disease of the ductless glandular system, and arrays himself against the opinions advocated by *Anton* and others, that there is also an infantilism that is dystrophic ectoglandular, independent of a disease of the endocrinous glands.

We see then there is hardly an idea in the medical literature concerning which there is more confusion than concerning infantilism.

The name infantilism can surely readily give occasion to misunderstandings because in any kind of inhibition of development, infantile features may be retained. I believe, however, that a clear definition is possible if we limit ourself to the thought that the childish organism is characterized not alone by the still undeveloped genitalia and the childish mentality, but, as already *Breus* and *Kolisko* mention, by definite childish dimenions.

**Definition.**—We may therefore briefly define a pure infantilism as a *standing still at the infantile stages of development, considering especially the following factors: the genitalia and the vita sexualis remain undeveloped*, or develop deficiently; and the same is true of the *secondary sexual characters; the involution of the lymphatic apparatus* is deficient, the growth is deficient, *ossification*, that is the appearance of the bone-nuclei and the *closure of the epiphyses* is delayed, and the *childish dimensions* of the body are retained wholly or in part; that is the lower length of the body equals the upper length or, what is commoner, exceeds it only a little, the form of the pelvis is neither [of the] masculine or feminine [type], but infantile, and finally the *psyche remains behind* [in development]. Such individuals show throughout no gross defect in intelligence, but their minds remain childish.

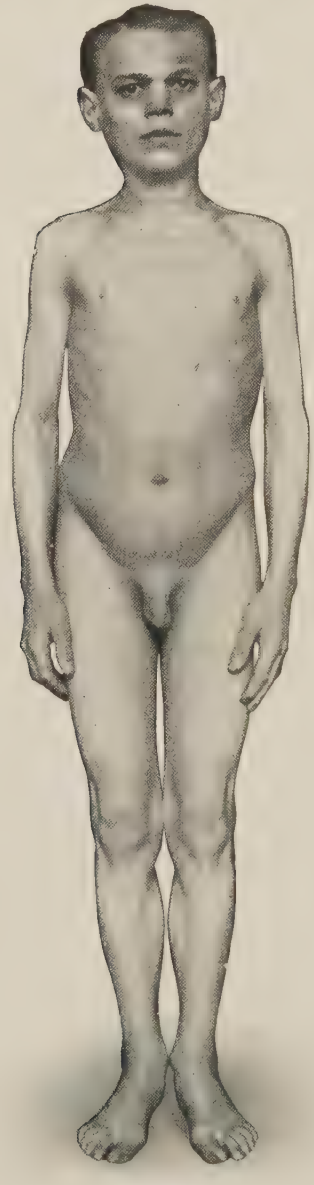
FIG. 81.—True infantilism (Observation LVI).

Important for the definition of infantilism are the following considerations, which serve to render precise the position of the ductless glandular system in the pathogenesis of infantilism. If the infantilism comes about through a standstill of the entire organism at a childish stage of development, then it is intelligible that also the sexual glands do not develop further. Up to the present however we have not sufficiently considered that the sexual glands occupy a separate position in the ductless glandular system, in that, though they functionate from early youth and influence the development of the organism, yet they attain their complete maturity only at the age of puberty; the other ductless glands are already fully developed in the new-born. At the same time, the remaining behind of the development of the sexual glands in infantilism is only a subordinate symptom of the entire clinical picture. We therefore do not find in infantilism such deep-going developmental disturbances as in eunuchoidism. The *genitalia are quite childish and the sexual glands functionate like the sexual glands of children,* while in eunuchoidism the sexual glands eventually do not functionate at all or slight islands of the sexual gland tissue have developed further, corresponding with the age, whereby there occurs an entirely insufficient function, a function that, on account of the faulty development of the accessory apparatus, is lacking; thus we see that the sexual glands of infantilism or the infantile genitalia are essentially different from those of eunuchoidism.

Thus if true infantilism comes about through the standing-still of the whole organism at a juvenile stage of development, the ductless glandular system remains just as childish as the skeleton or the hematopoietic apparatus or the central nervous system; therefore the inhibition of the ductless glandular system is only coordinated with that of the entire organism; as, if these premises hold good, we are not justified in classing infantilism with the primary ductless glandular diseases; on the other hand, it does not then seem to me justifiable to designate as infantilism sharply delimited clinical pictures that depend on a primary disease or developmental disturbance of a definite ductless gland, pictures such as juvenile myxedema, juvenile hypophysial dystrophy, or eunuchoidism.

Before I enter into the symptomatology of true infantilism and the basis of the view just expressed, I would like to report some typical cases of true infantilism.

*Observation LVI.*—J. H., twenty years old. At the age of seven years, commotio cerebri through fall from a tree. Present manifestations of a benign pyloric stenosis with dilatation of the stomach and hypersecretion. For one-half year tetany.

Total length, 142½ cm.; lower length, 69 cm.; span width, 143 cm.

The patient looks like a boy thirteen years old. Facial expression and psychical attitude entirely childish. Abundance of hair on head. Beard hair absent, hair in the axillæ and on the mons Veneris absent, soft downy hair on face. Penis small. Both testicles small. No libido, rarely weak erections that have appeared only recently, no ejaculations. The epiphysial junctures of the skeleton of the hand are almost all still open. For two years tetany, at the close of which slight manifestations of hyperthyrosis.

*Observation LVII.*—W. K., eight years old. Entrance into the clinic Nov., 1910. At the age of four years gradual deterioration of the gait. The child also remained backward mentally, and repeated for the third time his first class in school.

Typical progressive muscular atrophy, the description of which we may omit here.

Typical length, 117 cm. Circumference of head, 51 cm. Circumference of breast, 57 cm. Circumference of abdomen, 55 cm. From coracoid process to olecranon 25.5 cm. from iliac spine to internal malleolus 56 cm.

Both lobes of the thyroid distinctly palpable.

The tongue is large, always is seen to a certain extent between the teeth. Root of nose not retracted, skin everywhere elastic, feels moist. Cryptorchidism. Pilocarpine 0.01 gm. elicits minimal sweats, minimal salivation.

0.001 gm. adrenalin shows strong action on the pulse and on the blood-pressure, distinct diuretic action, no glycosuria.

Leucocytes, 9400, of which:
Neutrophiles, 55.1 per cent.
Large mononuclears, 8.3 per cent.
Lymphocytes, 33.3 per cent.
Eosinophiles, 3.3 per cent.

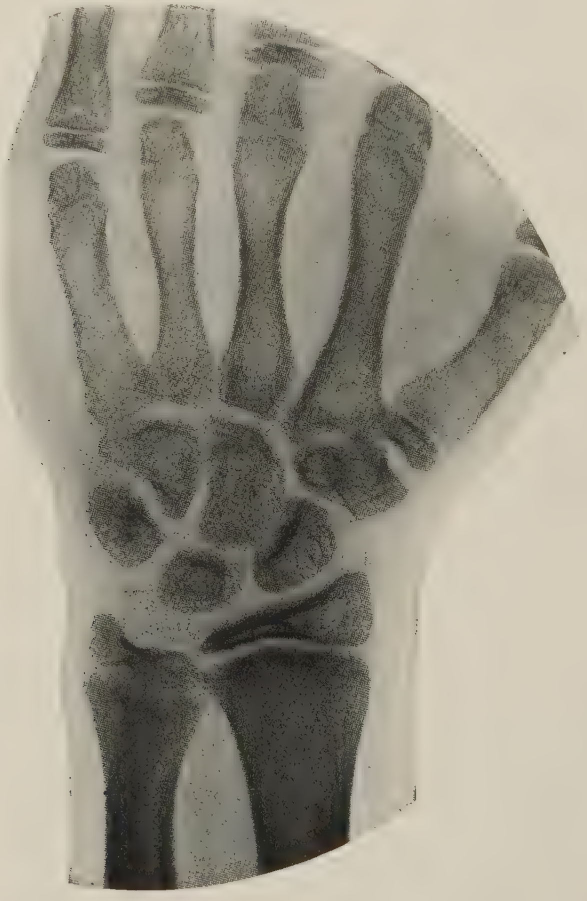

FIG. 82.—X-ray picture of the hand in true infantilism (Observation LVI). Delay of the closure of the epiphysial junctures.

From Nov. 14 on, one thyroidin tablet a day. On Dec. 18, 0.001 gm. adrenalin. Strong action on the pulse and blood-pressure; now 1.43 gm. sugar in the urine.

Under the influence of the thyroidin medication which now has lasted about six weeks, the pulse increases hardly at all, no manifestations of intoxication.

On entrance the X-ray examination of the skeleton of the hand showed the following: The distal epiphysis of the ulna, which should be deposited normally at seventh year, is here entirely absent.

The bone nuclei of the skeleton of the wrist are abnormally small.

At the end of a six weeks' thyroidin medication X-ray examination was again made, without showing any change worthy of mention.

In this case we are dealing with a typical progressive muscular atrophy, setting in early and associated with an inhibition of development. This is both physical (abnormal smallness, cryptorchidism, etc.) and mental. The large tongue gives rise to a thought of myxedema, but on careful searching no other signs of myxedema were found. Six weeks of the thyroidin medication causes no acceleration of ossification.

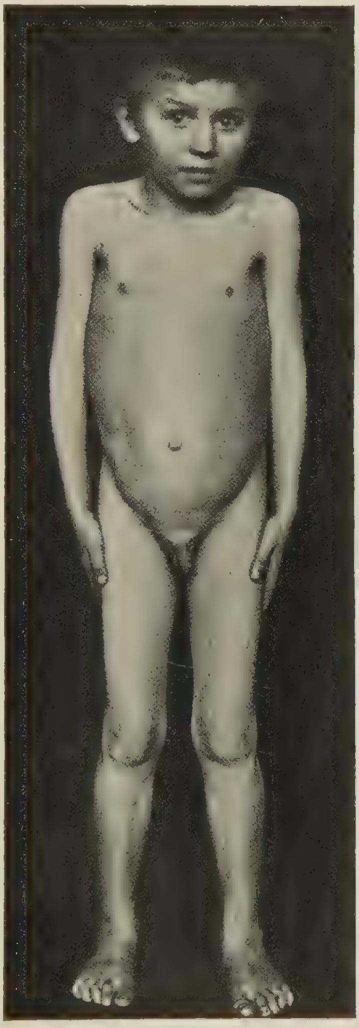

FIG. 83.—Infantilism in progressive muscular atrophy.

*Observation LVIII.*—R. R., twenty years old. Entered May, 1912. Several cases of tuberculosis in the family. The girl learned to walk only three years ago. Since childhood conjunctivitis eczematosa. From youth she has remained behind in growth and in mental development; at present she has the psyche of an eight- to ten-year-old child. Although, on account of her eyes, she never went to school, she can read and write and takes an interest in household affairs.

127 cm. tall. Span width, 128 cm. Lower length (ant. superior spine to ext. malleolus) 63–½ cm.

Very sparse growth of hair in axillæ and on the genitalia.

Adenoids in nasopharyngeal space. Glands of the neck, the elbow, and the groins somewhat enlarged. Slight horizontal furrowing of the teeth. Slight saber-sheath form of the bones, but otherwise no signs of severe rachitis.

The mammæ on both sides developed distinctly, little glandular substance palpable. First menstruation two days ago, weak.

Leucocytes, 7700, of which:

Neutrophiles, 61 per cent.

Lymphocytes, 32 per cent.

Large mononuclear, 5 per cent.

Eosinophiles, 2 per cent.

X-ray examination. Sella turcica normal, no peribronchial lymph glands.

Coarse nystagmus on both sides, the eye grounds show medullated nerve fibers, otherwise they are normal.

X-ray examination of the skeleton of the hand. The ossification corresponds to about that of a fifteen- to sixteen-year-old individual.

*Observation LIX.*—B. B., fourteen years old. Entered May, 1912. It was stated that in the first year the head and abdomen were very large, later good development, could walk at two years, speak at three. Remaining behind in corporeal development, especially since the first year of life. Mental development fairly good. Psyche, childish. Length of body, 111 cm., lower length, 62 cm., span breadth, 113.5 cm., length of arm, 38 cm.

Slender, weakly child, thin, looks like a child eight years old. Pallid. The head, relatively large (circumference, 54 cm). Frontal protuberances, somewhat prominent.

Adenoid vegetations in nasopharyngeal space, tonsils enlarged; in the neck, in the groins, everywhere, are palpable glands up to the size of a bean.

Distinct parallel furrows on the incisor teeth of the lower jaw. Slight form of pectus carinatus. Some lordosis of the lumbar spine. Slight affection of the apices of the lungs on both sides.

Erythrocytes, 2,800,000,
Hemoglobin, 60 per cent.
Leucocytes, 10,400, of which:
Neutrophiles, 52.0 per cent.
Lymphocytes, 41.1 per cent.
Large mononuclears, 2.5 per cent.
Eosinophiles, 4.0 per cent.
Mast cells, 0.5 per cent.

Slight poikilocytosis. X-ray examination. Vault of cranium thin. Sella turcica normal. No basis for thymus-rest. Right divergent strabismus, both papillæ somewhat washed out and pale, otherwise eye grounds and vision normal.

X-ray examination of the hand; the skeleton of the hand about corresponds with that of a ten-year-old boy.

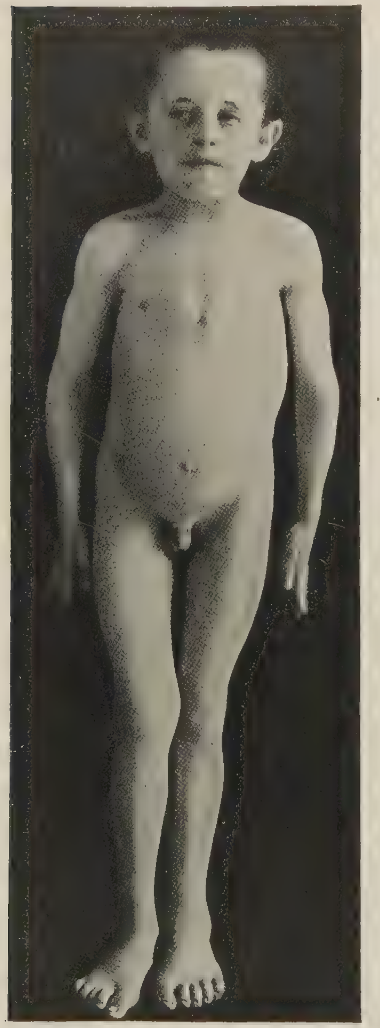

FIG. 84.—Infantilism (Observation LIX).

**Symptomatology.**—Ordinarily the disturbance in growth in true infantilism is very significant. Thereby the skeleton shows a retention of the childish dimensions, that is the lower length does not exceed the upper length, or exceeds it only a little. The head is relatively large, the bones are slender, the navel is low, the pelvis is neither masculine nor feminine, but infantile. The occurrence of the bone-nuclei and the closures of epiphyses are delayed.

The genitalia remain at a child's stage of development, they have the size and dimensions of a child's genitalia; thereby we are not dealing here with a falling away of the genital function, but with a function which corresponds with that of years of childhood. Correspondingly there is a remaining behind of the secondary sexual characters. Also the vita sexualis is that of a child.

The lymphatic apparatus shows deficient involution. We find therefore commonly a relatively great count of lymphocytes in the blood, on which account there is not necessarily present a status lymphaticus, although it is not improbable that the damaging that produces the infantilism also often leads to a status lymphaticus. Also the anemia that is not rarely found in infantilism can be regarded as a direct consequence of this deleterious influence.

The hair of the head is usually abundant, the hair on the trunk is mostly absent, not always entirely. The hairiness of the pubis and the perineum is mostly very sparse or is absent. The same holds good for the hair in the axillæ.

The internal organs are mostly normal, so far as illnesses, occurring in early years, have not led them to infantilism. The vascular system seems in the most cases to show a slight grade of hypoplasia. Also the blood-pressure often lies on the lower borders of the normal.

I am not aware as to the existence of investigations as to the respiratory metabolism. In the cases that I investigated the tolerance limits for carbohydrates approximate the normal. Functional testing of the vegetative nervous sytem sometimes showed slight diminution of the excitability. To this not much importance can be attached.

Characteristic for true infantilism is the retention of the childish features. We find the childish logic, the childish instinct for imitating, a certain anxiety and non-independence. For example the case reported by me (Observation LVI), acted like a boy when at his visits he was scolded for not having collected his urine. By the grown people of the clinic he was treated like a child. *Ziehen* points out in this regard that in infantilism the individualizing association characteristic of children is retained. Also the psychical inhibitory apparatus is only deficiently developed. *Di Gaspero* attaches especial value to the retention of the childish ideas of value, and the suggestibility of children. A careful description of the psyche of infantilism is furnished by *G. Anton*. "The mimicry, gesticulations, physiognomy, corresponds to childish age phases. Also pitch and modulation of the voice. For the most part there is absent the childish gaiety and freedom, often there comes to expression feelings of insufficiency, timidity, and peevishness." For the most part the attention may be readily drawn, but is readily deviable. Constant concentration is not to be attained. Complicated sense impressions produce a feeling of unpleasantness. "Often therefore they have acquired a routine in which complicated impressions and tasks are slipped by; their selection tends to the primitive, the simple." I have attached value to reproducing the description of *Anton*, because it is enough to show that the psyche of persons with infantilism is essentially different from that of eunuchoids.

**Forms.**—According to the intensity of the noxious agent that is to blame for infantilism, do different forms of this condition occur, from the quite excessive forms which in their corporeal and mental development remain little children all their lives, to the poorly pronounced formes frustes. Very important for the differentiation of the forms is also the consideration of the phase of development at which the noxus set in. "Every age period has its infantilism" (*di Gaspero*). When the noxus sets in relatively late there results a form which has been termed "juvenilism." In this the skeleton is no longer purely childish. The genitalia are relatively well developed, etc. We find very commonly the juvenile form of psychic infantilism in ordinary life (*Anton*). According to whether the inhibition of development has affected the more the skeleton, the psyche, or the genitalia, etc., we may speak of partial infantilism. An instructive example of a juvenilism is furnished by a case briefly reported by *Apert* and *Rouillard*. In a thirty-eight-year-old man who had developed normally up to his sixteenth year, there occurred in the wake of a typhoid fever a remaining behind in corporeal and sexual respects, at this developmental period. There were present no signs of eunuchoidism. *Apert* and *Rouillard* attribute this inhibition in development to the thyroid gland. As no signs of myxedema were present, I would dissent from this view.

The excessive form of infantilism might well coincide with the hypoplastic dwarf of *Breuss* and *Kolisko*. *Breuss* and *Kolisko* indeed state that in the hypoplastic dwarf only the height is childish, the other dimensions only in part childish. Probably in such individuals the disturbance has its onset in fetal life or in early youth.

**Etiology.**—The etiology of infantilism is very manifold. The most divergent toxic and infectious deleterious agents are blamed. Alcoholism, saturnism, nicotine-poisoning—agents that may also have affected the parents—further malaria, pellagra, syphilis (a fine example is furnished by *Peretz*) tuberculosis, abdominal typhoid in early youth (see the case of *Apert* and *Rouillard*); polyserositis (*v. Neusser*), deficient development of the cardiovascular apparatus (*Hödlmoser* has communicated a pronounced pertinent case that was only 125 cm. tall with a lower length of 66 cm.), and further cardiac defects acquired in early youth (*Gilbert* and *Rathery*) (and in this nanisme cardiaque the genital disturbance may eventually become less pronounced), and the traumata that may affect the children in early youth (the case J. H., Observation LVI, suffered a commotio cerebri at the age of seven years). *Joffroy* described two cases of paralysis générale juvénile with pronounced infantilism. I have reported such a case above (see Observation LVII, W), further it has been supposed that unfavorable conditions of life, and conditions of nourishment in early life are causal factors, and also disturbances of nutrition, chronic diarrheas, etc., existing since early life (see later concerning pancreatic infantilism). The position of the cases with hydrocephalus does not seem to me assured as yet, in these cases consideration must be given especially to signs of hypophysial insufficiency, especially the distribution of fat.

Also the liver diseases acquired in early life may lead to infantilism. *Lereboullet* described a case in which he ascribed hypertrophic biliary cirrhosis of the liver as the cause of the infantilism. The following case also perhaps belongs in this group.

*Observation LX.*—G. A., twenty-one years old. Entered Nov., 1909. Since early youth strong imbiber of alcoholic liquors. In 1906, he fell in the water, after which pneumonia, later pleurisy. Since that time has not grown much. For about two years, swelling of the abdomen, edema of the legs, and enlargement of the liver. The ascites subsided, the liver remained large and painful.

According to his statement, for about three years after the time of puberty the patient had libido and erections, that later ceased. Never pollutions, never cohabitation.

Very considerably enlarged liver, painful to pressure, pole of the spleen palpable, heart dullness somewhat enlarged to left and to the right. Extra-systoles, no ascites, no albumen.

The physiognomy is juvenile, no beard, no axillary hair, sparse growth on Mons Veneris. Testicles and penis of normal size.

**Differential Diagnosis.**—If we confine ourselves to the symptoms just described, the delimitation of true infantilism from the diseases of the ductless glands associated with infantile features is not difficult.

And yet on closer examination of the individual cases described under the same infantilism we find that very frequently later authors confuse infantilism with diseases of the ductless glands. Thus I would hold that in the communication of *Richon* and *Jeandelize* the first of the cases described was probably an eunuchoid, the second a cretinoid and the third perhaps a true case of infantilism. Another example: In the communication of *E. Levi*, I regard the first case as one of hypophysial dystrophy, the second is difficult to classify, the third is perhaps a typical case of true infantilism.

I would detail somewhat more exactly the most important differential diagnostic features:

Let us begin with the delimitation from infantile myxedema. In the French school two types of infantilism are distinguished, the *Lorain's* type that on the whole is true infantilism, and second, myxinfantilism. When however we go back to *Brissaud's* original publication, we find that the characterization of myxinfantilism is very inexact. Here begins an error that has continued until the latest time, and that may be regarded as the chief cause of the prevailing confusion. *Brissaud* describes myxinfantilism in the following manner: The face is round, the lips are thick, the nose small, the cheeks are thick, the genitalia infantile, the thyroid gland small, the ossification is delayed, dentition is retarded or fails, the neck is short, and there often exists lordosis of the lumbar spine; among the individuals belonging to this type there also are those whose health may be very good. *Brissaud* held the opinion that in the majority of cases myxinfantilism is not an état morbide and he refers also partial infantilism to an insufficiency of the thyroid gland. As an example he quotes the cases of two sisters of whom the elder looked to be about three years younger than the other and showed an entirely childish habitus. Also that of a boy of sixteen years, who looked as if he were eleven years old, and whose psychical attributes corresponded with that of the latter age. At the age of ten years of life he had sustained an inflammation of the throat and a swelling of all lymph glands; *Brissaud* here regards it as established that at that time the thyroid gland was affected. The third case that *Brissaud* cites is, on account of the inaccurate description, hard to classify. I need hardly detail more intimately that the belonging of the cases cited to infantile myxedema is at least uncertain, even unlikely. A priori we may withdraw from consideration, however, the classification on the etiological basis, according to the assumption of *Brissaud*, that a severe disturbance of development could depend on a thyroid insufficiency, without other symptoms of myxedema being present. The inhibition of ossification alone, on which some stress has been laid, is no certain sign of thyroid insufficiency. *Meige* and *Allard* point out, it is true, as the foundation of this assumption, a case of typical *Lorain's* infantilism in which ossification had advanced much further than in a case of myxinfantilism. *E. Levi* showed, however, that in the type *Lorain* the ossification is much delayed as compared with that of a normal individual of this age. It is certain that also in true infantilism there exists a certain inhibition of ossification, and that even a certain acceleration of ossification may follow thyroid gland therapy. But this does not furnish a certain demonstration of the thyrogenic pathogenesis of such cases, for, as *Ferranini* already mentions, the stimulation of the metabolism through the administration of the thyroid gland may help somewhat. To-day, when the manifestations of thyroid gland insufficiency in childhood are so carefully studied, we would require unconditionally sure signs of childish myxedema if we were to call a case myxinfantilism. The delimitation of true infantilism from severe forms of childish myxedema is indeed readily made. The mitigated forms may be distinguished from it by the presence of myxedematous alterations of the skin, thickening of the tongue and lips, the umbilical hernia, disturbances of intelligence, apathy, and especially the result of thyroid gland therapy.

Naturally there also occur mixed cases. Signs of thyroid gland insufficiency may be added to those of true infantilism, temporarily or permanently. Perhaps such a case is described by *Dupré* and *Pagniez*. Here a myxedema began at the fifteenth year of life in a case of true infantilism.

Also the delimitation of true infantilism from eunuchoidism is not difficult in most cases. It is quite unintelligible how *Peritz* can regard eunuchoidism as the purest form of infantilism. In eunuchoidism we have an isolated severe disturbance of the development of the sexual glands, and here the analogy with eunuchoidism ends, the dimensioning of the body [in eunuchoidism] has nothing in common with the childish dimensions. (Significant predominance of the length of the extremities and small head.) Also the psyche of typical eunuchoids is not childish throughout. The feeling of absent virility here often leads to timidity and eventually to deep mental depression, while the childish features [of the disease] are absent. *Wolff*, just as has *Peritz*, has spoken against the designation eunuchoid, with incorrectness. Of the four cases that *Wolff* communicates, case 3 probably belongs to true dwarfism, associated with genital disturbance (*Paltauf's* type). He is certainly not an eunuchoid, but a mixed form between true dwarfish and infantilism. The other three cases are however typical infantilism, distinguished from true eunuchoids by their childish psyche and by the proportioning of their bodies.

The delimitation of true infantilism from typical juvenile hypophysial dystrophy is easy. In this too is found the disturbance in growth, but to the disturbance is added the typical distribution of fat, and the disturbance of development of the genitalia is much more severe and eventually retrogressive. There are also present symptoms of increased intracranial pressure. I would here point out, as I have already in the chapter on the hypophysis, that it is quite unjustifiable to refer off-hand to the hypophysis, a disturbance of growth, if other manifestations of hypophysial insufficiency are not otherwise present. *Aschner* has described a sixteen-year-old dwarf girl, 132 cm. tall; the ossification and dentition were delayed, her proportions were childish, and psychically and intellectually she was childish. She became pregnant in consequence of a rape. This indeed does not speak much against existing infantilism of the genitalia, as under circumstances children may become pregnant before the onset of menstruation. *Aschner* rejects the expression infantilism as indefinite, and regards the cause of the disturbance of growth as hypophysial without furnishing any evidence for his opinion. I regard this case as true infantilism or as a hypoplastic dwarf.

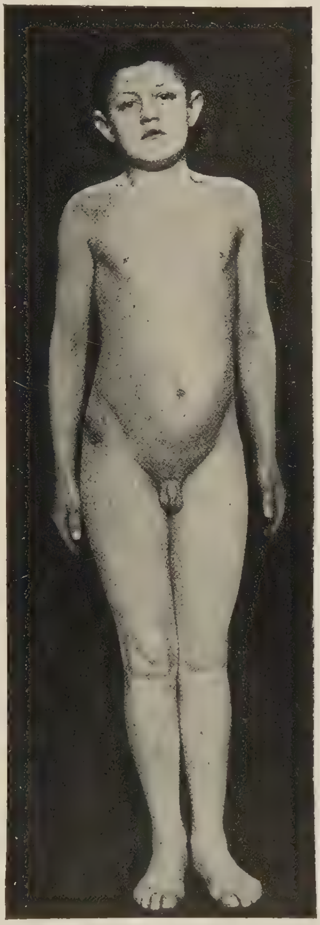

FIG. 85.—Mixed form between true infantilism and dystrophia adiposo-genitalis.

Naturally there are numerous cases that constitute transitional cases between true infantilism and the hypophysial or eunuchoid form of dystrophia adiposo-genitalis. As example I cite the following:

*Observation LXI.*—B. A., sixteen years old; entered the clinic February, 1911. Father dead. Mother had had lues before the child's birth. Wassermann still positive. Also the boy gives a positive Wassermann. The boy learned to speak and walk as late as three years old. At the age of eight, a fall from a second story. Unconsciousness for ten minutes, and, according to statements, no after effects.

The boy is small, length of body 142.5 cm. Lower length 82–½ cm. Psyche childish, corresponding to that of a boy thirteen years old.

Slight sinking-in of the bridge of the nose: *Hutchinson's teeth.* No hair at all in the axilla and on the pubis. On the breasts slight collections of fat, collection of fat on the mons Veneris. Penis very small, testicle small, in the scrotum on both sides.

Scoliosis of the thoracic spine to the left; left pupil twice the size of the right; both fail to react to light, patellar and Achilles reflexes very lively. Hyperesthesia of the whole left side of the body, sharply cut off at the medium line. Nervous condition otherwise O.K. Fundus normal; to X-ray examination sella turcica normal.

The epiphysial joints of the hand-skeleton are wide open, and the sesamoid bones as yet show no bone-nuclei.

Diagnosis.—Infantilism + dystrophia adiposo-genitalis of a slight grade, in hereditary lues.

In this case of hereditary lues the excess of the lower length over the upper length militates against pure infantilism. Further, the eunuchoid distribution of fat is doubtlessly indicated. The developmental disturbance of the sexual glands is somewhat more pronounced, and is perhaps of hypophysial origin (congenital lues, different symptoms on the part of the nervous system); on the other hand these symptoms are slight in comparison with the inhibition of growth, and the psyche is decisively childish.

Just a few words concerning the so-called *pancreatic* infantilism. *Bramwell* and later *Rentoul* have described such cases. In the case of *Rentoul* we are dealing with a girl eighteen years old, who from youth suffered with diarrheas (fat stools?). She grew slowly up to the eleventh year, and then, with regard to growth, remained at a standstill to the age of eighteen. She looked like an eight-year-old girl. The stools improved very much on the administration of pancreatin; she now increased rapidly in weight and grew in four months about 2 in. I do not regard as appropriate the term "pancreatic infantilism." Thereby we might be induced to attribute infantilism to a disturbance of the internal secretion of the pancreas, although in these cases we may be dealing with true infantilism brought about through nutritional disturbances. When the nutritional disturbance improves, the retardation of the development may in part be mitigated. Disturbance of the internal secretion of the pancreas does not lead as far as is known to infantilism. Youthful diabetics do not show infantile features. In several cases of juvenile diabetes I have convinced myself that ossification does not remain behind.

The vegetational disturbances in early childhood through damaging of the suprarenal cortex are as yet too little investigated that we can delimit them from infantilism. I refer to the chapter on this subject. Apparently hypoplasia of the chromaffin tissue likewise does not lead to true infantilism. Probably such cases belong to the so-called hypoplastics of *Bartels* or to true status lymphaticus.

**Pathogenesis.**—As I already mentioned at the beginning, the tendency is coming more and more to the fore to regard the cause of infantilism as a disturbance of the ductless glands, or in a disturbance of ductless glandular correlations; the disturbances of the correlations is chiefly a favorite modern catchword. This opinion I cannot share. I regard true infantilism as the vegetative disturbance dependent on an inhibition of development of the whole organism. Only the developmental retardation of the ductless glands is coordinated with that of the entire organism. Hence there is found no disturbance of correlation among the ductless glands, but a function of them graduated for an organism that remains childish, a function fully suited for the childish conditions. In true infantilism, also the sexual glands functionate—for signs of eunuchoidism are absent—but they functionate like those of children. According as the damage has occurred in the fetal, the infantile, or the juvenile organism, do there occur fetalism, infantilism, or juvenilism.

A damaging that in youth acts electively on the ductless glandular system, and injures it severely must according to my view, lead to a vegetational disturbance that is similar to multiple ductless glandular sclerosis. It would condition cachexia and premature senility, but not infantilism.

The conception of infantilism agrees with that of *Anton*, who rules out dystrophic infantilism from the true ductless glandular diseases. The difference consists only in the fact that I limit the idea of infantilism still more and do not class with it the true ductless glandular diseases of childhood.

I need hardly mention again that this view holds only for the typical forms of infantilism. There are perhaps as many transitional forms as typical forms that pass over into the ductless glandular diseases. These transitional forms may exist between infantilism and various other diseases—hypophysial or eunuchoid dystrophia adiposo-genitalis, or pronounced status lymphaticus, with marked hypoplasia of the chromaffin tissue, or true myxedema or cretinism, or other vegetative disturbances yet to be described (true dwarfism, mongolism, etc.). I believe it is better to be precise in the delimitation of true infantilism as in this way the transitory forms that are so frequent, are made easier to recognize and easier to analyze.

**Prognosis.**—The later fate of true infantilism has not as yet been thoroughly studied. It is known, however, that the patients show an especial disposition for various diseases and mostly die prematurely (*di Gaspero, W. A. Freund, Hegar, et al.*). Especially does tuberculosis reap a rich harvest among them. Also their mentality seems to suffer under the rough influences of life and severe conflicts.

**Treatment.**—The treatment in the true forms as yet is almost hopeless. Thyroid gland medication, hypophysis medication, etc., may yield slight results in the mixed forms. True infantilism usually shows a lower tolerance for thyroid preparations.

## II. TRUE DWARFISM

True dwarfism as a proportioned nanism may be rather well delimited from the other vegetative disturbances that I have thus far described or will hereafter describe in this chapter; as all of these with the exception of true infantilism are disproportioned nanisms, while in true infantilism the childish dimensions are retained. In spite of the fact that we are considering true dwarfism in this connection, it constitutes no uniform affection. Indeed attempts have been made to distinguish two different types of true dwarfism that differ from each other in important points and perhaps are also to be separated etiologically. There exists, however, as we shall see, all possible transitions between these types. As long as we do not know anything certain concerning the etiology of true dwarfism a satisfactory terminology for all the cases that belong in this group is not possible.

**Historical.**—In this short exposition I would not enter into the descriptions that exist in the old literature. It is to be supposed that among the numerous dwarfs that in former times were retained at the courts of nobility on account of curiosity or that were exhibited in the show booths [as freaks] there were some that were true dwarfs. The descriptions of these are, however, very inexact. Therefore I shall limit myself to the fewer and more careful communications in the later literature. The first exact description of the skeleton of a true dwarf originates with *A. Paltauf* in the year 1891, while *v. Hansemann* was the first to separate the two types of true dwarfism. *v. Hansemann* distinguished a nanosomia primordalis and a nanosomia infantalis. In the latter at the time of birth the individual is of normal size. Growth ceases only later, the epiphysial junctures remaining open; often the individual remains infantile. This form is identical with that described by *Paltauf*. The primordial dwarf is small from the beginning, although his development, apart from the smallness, proceeds in the normal manner. He is, therefore, a veritable diminutive human being; *Sainton* and *Launois* distinguish this true dwarfism from the other vegetative disturbances, without, however, considering the other type. Also *E. Levi*, who has published a thorough study of this form of dwarfism, has considered *Paltauf's* form insufficiently.

*A. The Primordial Nanosomia.*—An excellent example of this form is the case described by *Virchow* and later by *v. Hansemann*. It was that of an individual twenty-two years old (who at the age of eleven years was investigated by *Virchow*) who was 114 cm. tall. He was entirely well proportioned, the intelligence was well developed, the genitalia were well developed, except that cryptorchidism was present. The epiphysial junctures had ossified. At birth he had weighed only 500 gm. This was doubted by *v. Hansemann* although it is certain that at the birth the parents were impressed with the abnormal smallness. It was the fifth child of twelve, and the first dwarf. Later three dwarf children followed, but they did not attain a high age. Between them there were births of normal-sized children, that later also developed normally.

To the primordial dwarfs belong also the dwarf family Magri, studied by various Italian authors and exactly described by *Taruffi*. The husband and wife Magri were entirely normally developed; of thirteen children eight survived, five were of entirely normal size, three extraordinarily small. Of these there was a girl 102 cm. tall, in whom menstruation occurred late but who was otherwise normal. A boy of 110 cm. of bright temperament, but bad character, married in his twenty-sixth year a woman of normal size and had by her two children—a boy who was of normal size and a girl who was apparently a dwarf. The third dwarf child of the Magri husband and wife was 109 cm. tall. All three Magris grew taller very slowly.

Very exactly studied are also the cases of *Levi*. These I shall now describe more in detail. The first was a forty-nine-year old man, 109 cm. tall. The lower length was shorter than the upper length. The individual was small already at birth; the genitalia, the secondary sexual characters, and the intelligence developed fully. At the age of twenty, he married a woman of normal size, who after eight years bore a child of extraordinary smallness. Two years later there followed a still smaller child, who died at the age of ten years. At the age of forty-nine years the man was still sexually active. The second case of *Levi* was that of a twelve and one-half-year old son of case I. He was 77 cm. tall and very intelligent. The third case was that of a thirty-three-year-old man, 111 cm. tall, weighing 25 kg. The lower length was 64 cm.; the father was very small, the mother of normal size. The stunting of growth became prominent especially between the eighth and the tenth year. At the age of twenty-eight he married, and his child at two years old of extraordinary diminutiveness. In all cases the ossification and the closure of the epiphyses corresponded to the age. *Levi* also emphasizes the fact that these cases, like the dwarf described by *v. Hansemann*, showed a slight retraction of the back of the nose and a slight degree of drum-stick fingers.

The primordial dwarf is hence characterized by the fact *that the dwarfism exists already at birth, that apart from the smallness the development proceeds normally*, and that the genitalia, the ossification and the epiphysial junctures, and the intelligence develop rather normally. According to *Hansemann* "infantile" features are found only here and there, for example, cryptorchidism, or in the case of *v. Hansemann* enlarged thymus, or retention of the lobules of the kidney, abnormal length of mesocolon, funnel-shaped proximal end of the appendix, etc. *Levi* points out the slight retraction of the root of the nose and the slight degree of drum-stick fingers.

*B. Paltauf's Dwarf.*—*A. Paltauf* described the skeleton of a dwarf who died at the age of forty-nine years; all the epiphyses were open. The individual was 112.5 cm. tall; he came from an entirely normal family; the intelligence was normal (he had taken part in two campaigns). He had twenty-eight erupted teeth; the thyroid gland was normal. *A. Paltauf* believes that in this case he was dealing with a nanosomia sui generis that depended on an earlier stage of the formation-age on account of the bones remaining at a standstill in development. Also the deformed cartilaginous base of the skull had ceased its growth, while the bones laid down in membrane grew further, thus allowing the normal development of the brain; although a slight cretinoid facial expression was thereby brought about. The skeleton is proportioned, shows, however, childish dimensions, the upper and lower lengths approximating those of a child (*Breus* and *Kolisko*). Such individuals may suddenly begin to grow again. *A. Paltauf* cites two instances, the English dwarf Jeffery, who began to grow again at the age of thirty years, and the Polish dwarf Borwilawski. The brothers and sisters of the latter were also dwarfish, but his children developed perfectly normal. I shall limit myself to the citation of the well-observed cases.

The case of *Schaafhausen* was a sixty-one-year-old man, 94 cm. tall; several members of the family were also dwarfish, the genitalia were infantile, the facial expression childish. The sutures of the skull were all ununited, the epiphyses nearly all. The observations of *Schauta*, *Ranke*, and *von Voit* perhaps belong here also.[1] *Hitschmann* describes a thirty-five-year-old man who came of normal family and who developed normally up to the age of five years. Then growth was retarded, although he did grow up to the twenty-fifth and twenty-sixth years. He was 108 cm. tall, beardless, the voice did not change, the thyroid gland was normal. X-ray examination showed epiphysial junctures open 1½ cm.; the intelligence was normal. He was an actor with a Lilliputian troup.

A second case of *Hitschmann* was that of a twenty-two and one-half-year-old singer; the inhibition of growth began at the tenth year. She was 125 cm. tall, slender, the intelligence was normal, the epiphyses were for the most part ununited.

*Joachimsthal* describes several members of a Lilliputian troup, among whom was an individual thirty years old, in whom the stunting of growth had begun in the third year; at fifteen years of age, she was 90 cm. tall, and at thirty years 100 cm. tall. The facial expression was childish, the voice had not changed and the axillary hair was absent. All epiphysial junctures were open. The bone nuclei were about as well developed as those of a ten-year-old child. In an individual thirty-six years old the inhibition had begun at the age of seven. At the age of twenty-two he was 105 cm. tall, and at the age of thirty-six, 128 cm. tall, the epiphysial junctures were open, the bone nuclei had developed further. In an individual thirty-three years old the inhibition had begun at the age of ten years, at twenty years he was 109 cm. tall, at thirty-three years 134 cm. tall; in a woman thirty years old the inhibition had begun at the age of eight years, at nineteen years she was 103 cm. tall, now 132 cm. tall. To the *Paltauf's* type belongs probably the celebrated dwarf *Helen Gübler* called the "Puppenfee" [doll fairy]. At birth she was normal. She ceased growing at the age of six years, and at twenty years was 106 cm. tall.

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[1] The case of *His*, quoted by *Paltauf*, belongs to the endemic cretins, that of *Dalega* to the sporadic cretins.

If we survey the cases quoted, we find that the *Paltauf's* type may be characterized thus: *At birth the individuals are of normal size, and at first show a normal development. Only later, but at all events mostly in early youth, they suddenly cease growing.* The epiphysial junctures remain open, and in all cases there occurs a *quite slow further growth,* the inhibition being broken through in exceptional cases only. The development of the bone nuclei is in nearly all cases delayed only a little, the development of the intelligence is normal. *On the contrary the genitalia and the secondary sexual characters* remain behind almost always. The cause of this growth disturbance is as yet not known.

The typical *Paltauf's* dwarf differs essentially from an individual with true infantilism. In the latter condition not all the epiphysial junctures remain open, only the ossification is highly retarded, so that we find ununited only those junctures that tend to close the latest otherwise. Then too the psyche of *Paltauf's* dwarf is ordinarily not childish. I have therefore discarded *v. Hansemann's* expression "infantile dwarf" and have chosen the expression "*Paltauf's* type."

The distinction between the primordial dwarf and *Paltauf's* dwarf, on the one hand, and high-grade infantilism on the other hand serves only for the typical cases. It will readily be seen that transitional forms between the two varieties of dwarf and true infantilism occur. To quote some examples only. *Joachimsthal* describes among his cases two thirty-six-year-old individuals of 114 cm. and 116 cm. heights respectively. With these, growth has remained at a standstill at about the tenth year. We can therefore not classify them with the primordial dwarfs. The epiphysial junctures were, however, closed, and both menstruated regularly since their twentieth year. In a female dwarf with retained epiphysial cartilages the sexual organs were quite normally developed. She conceived, and at Cesarean section was delivered of a child above the normal in weight and size.

The circumstance that there are transitions between the primordial and the *Paltauf's* type does not mean that they both rest on the same etiological basis. It would be very easy to assume that in the primordial dwarf the noxus took its effect in fetal life, in *Paltauf's* dwarf, in postfetal life. This does not, however, explain the great difference in the relation of the genitalia. As will be seen by the example quoted, the familial hereditary occurrence is common to both types. In both types, too, the children of the person affected may develop normally.

There therefore does not seem to me to lie at hand any basis for considering true dwarfism as an affection of the ductless glandular system. I need hardly point out further that the thyroid is certainly entirely uninvolved. *Aschner* would indeed make the hypophysis answerable for dwarfism —certainly incorrectly—for all the symptoms characteristic of hypophysial dystrophy are absent.

## III. THE RACHITIC DWARF

Dwarfism may be the result of a high-grade rachitis developing in children. According to *Breus* and *Kolisko*, in addition to the inhibition of growth in height, there are found regularly also *curvatures*—under circumstances the bones are weak and flexible. "The disturbance of the periosteal ossification, in contradistinction to endochondral ossification, comes into the foreground." *Breus* and *Kolisko* also state that in such cases the epiphysial junctures can often remain ununited; *Gulecke*, however, reports three cases of dwarfism who had suffered severe rachitis in early life and yet showed on X-ray examination premature synostosis of the epiphysial junctures. *Gulecke* assumes that the epiphysial cartilages were severely damaged by the rachitis, and that then reparatory processes set in which led to premature ossification. In fresh cases the X-rays show washing out of the boundaries between the bone nuclei and cartilage, and at the site of the epiphyses broad light zones apparently representing excessively proliferated cartilage (*Joachimsthal*). The behavior of the epiphysial junctures and the bone nuclei thus vary according to the intensity of the process, according to the liveliness of the proliferation of the abnormal cartilage, and the reparatory processes. Rachitic dwarfism is characterized by *the never-absent signs of a previous rachitis and by the normal development of the intelligence and of genital sphere.*

## IV. CHONDRODYSTROPHY

### (*Achondroplasia*)

**Historical.**—Chondrodystrophic dwarfs were known already in antiquity. *Cestan* and *Meige*, who have concerned themselves with the historical study of this disease, refer to the pictures of the Egyptian god *Ptah* and the goddess *Bes*, in which typical cases of chondrodystrophy are exhibited. Also the statue of *Karakalla* and several pictures by *Velasquez* show typical chondrodystrophics. Formerly chondrodystrophy was regarded as congenital or fetal rickets (*Sömmering*, *H. Müller*, *Langer*, and *others*). *Virchow* described a chondrodystrophic dwarf that he regarded as a case of endemic cretinism. In France, *Porak* denied the assumption of achondroplasia as fetal rachitis and set forth that it was concerned with an affection of the epiphysial cartilages that sets in in fetal life. *Kaufmann* in his known monograph lines himself against *Virchow's* explanation, *Kaufmann* and later *Diederle* have done away for good with the conception of a thyrogenic disturbance, until *Kaufmann* originated the name chondrodystrophy, by which the condition is known in Germany. *Kassowitz* calls the disease "Mikromelie." But this designation is not precise, as there are different kinds of micromelie (shortness of the extremities) that have nothing to do with chondrodystrophy. (Osteogenesis imperfecta [*Vrolik*], phokomelie, etc.) and chondrodystrophy constitutes only one of these types. I refer the reader to the excellent dissertation of *Siegert.*

**Definition.**—*Chondrodystrophy is characterized by a growth disturbance of the cartilages at the ossification boundary of the cartilages, those of the long bones especially, setting in the earliest fetal life.* According to *Kaufmann* there is found microscopically either mucoid softening of the cartilages (*malacic form*), or only cessation of growth (*hypoplastic form*), or even considerable, but entirely disorderly, proliferation, which takes place in all directions instead of in the longitudinal direction, and thus leads to a moderate swelling out of the epiphyses (*hyperplastic form*). In older individuals, the cartilaginous zone of proliferation is bounded at the periphery by strips of connective tissue (*Diederle*). Thereby the periosteal bone formation is not inhibited, and may even be excessive, just as is the formation of bone nuclei in the epiphyses which may even show acceleration. The disturbance affects also the *bones of the skull that are preformed in cartilage, and the vertebral column, while the growth of the bones preformed in membrane is not inhibited.*

**Symptomatology.**—From this growth disturbance there results a skeletal formation characterized by the following points: The base of the skull is markedly shortened by the inhibition of growth and the premature synostosis of the os tribasilare occipitalis and the os basilare occipitalis, as first described by *Virchow.* There is thus brought about a marked retraction of the root of the nose, such as is not observed in any other growth disturbance. There are, however, rare cases of chondrodystrophy without this retraction. *Eichholz* has described three such cases belonging to one family. Then again the retraction of the root of the nose may exist, without there having taken place a coalescence at the synchondrosis (a case of *E. Langenbach*). The clivus is shortened—I here am following the description of *Breus* and *Kolisko*—the foramen magnum is very small; the base of the skull is most supernormally large; there occur also hydrocephalic skulls in which ossification is rather retarded so that the fontanelles persist abnormally long. The form of the sella turcica may be quite abnormal (confer Observation LXIII). If the subject lives after the period of childhood, the development of the brain and the intelligence is normal. The upper jaws are broad, spread far apart, the upper jaws markedly project. Dentition is entirely normal. The vertebral canal is narrowed, in the frontal diameter mostly, on account of premature coalescence of the nuclei of the arches and the bodies, but sometimes generally.

There exists lordosis of the lumbar spine and kyphosis of the thoracic spine. The thorax is narrowed in the sagittal diameter. In five skeletons of grown chondrodystrophic dwarfs, *Breus* and *Kolisko* found frontal stenosis[1] of the vertebral canal in every case. According to *Diederle* the narrowing may also be conditioned by hyperplasia of the cartilage. This was true in pronounced manner in both of *Lampê's* cases. In one of these the spinal medulla was markedly compressed on this account.

In chondrodystrophy the ribs are broad and coarse, and at the junctions of the ribs the cartilages are often swollen-up (pseudo-rosary), in such a manner that the bony part embraces the cartilaginous. Siegert describes a marked swelling-out at the part of the rib bordering on the capitulum costis, with sharp-angled bowing and fungus-like swelling out of the epiphysis; the sternum is broad and thick, body and xiphoid process are synostosed; the clavicles are short, and bent in the form of an S; the scapulæ very small, their borders coarse, the pelvis generally narrowed, its inlet kidney-shaped. The promontory [of the sacrum] projects markedly, the ilia are thickened, shovel-shaped with thickened borders. Most characteristic of the micromelic growth disturbance is the inhibition in growth of length of the extremities, which is the proper cause of the dwarfism of the individual. Under normal conditions the lower length begins to exceed the upper length already toward the end of the first year of life, and the difference becomes more marked as the years pass. In the disease under consideration however the *growth in length of the extremities remain so far behind that the relation of the upper length and lower length may reach* 2:1. As the periosteal bone-formation is not inhibited, the cortex of the diaphyses is very thick and *very marked places for the insertions of the muscles develop;* the muscles themselves are entirely normal, so that the chondrodystrophic dwarfs are very strong with regards to muscular force and are clever acrobats. According to *Breus* and *Kolisko* the fibula is less shortened than the tibia, so that it projects markedly below the lower end of the tibia, thus producing a varus position of the foot; the feet are shortened, also the upper extremities are essentially shortened, likewise the hand, the breadth of which is however normal; the shortened fingers stand apart from one another (main à trident, Radspeichenform). The ossification of the epiphyses proceeds very irregularly. The epiphyses themselves may, as *Siegert* mentions, sometimes be more hyperplastic, sometimes more hypoplastic, in the latter case embracing the diaphyses. The closure of the epiphysial junctures may occur prematurely, especially those of the metacarpal bones of the hands and feet; at other places, however, the epiphyses may close abnormally late. In the seventeen-year-old case I shall report later, the distal epiphysial junctures of the radius and ulna, and the proximal of the first metacarpal and phalanges are as yet wide open, so that examination of the accompanying X-ray picture will show that the head of the metacarpal bone is swollen out, extremely coarse, the epiphyses developed, in part—for example that of the radius. Hyperplastic and hypoplastic processes may often be seen in the same skeleton.

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[1] In German edition "sclerosis," according to the original article of *Breus* and *Kolisko* "stenosis."—*Editor.*

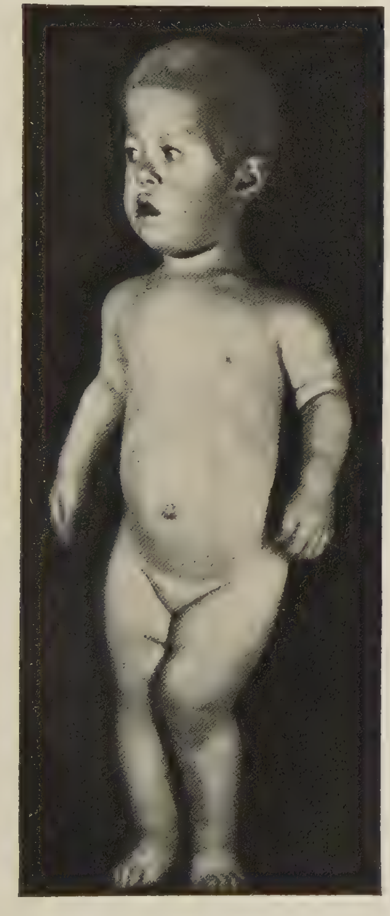

FIG. 86.—Chondrodystrophy (Observation LXII).

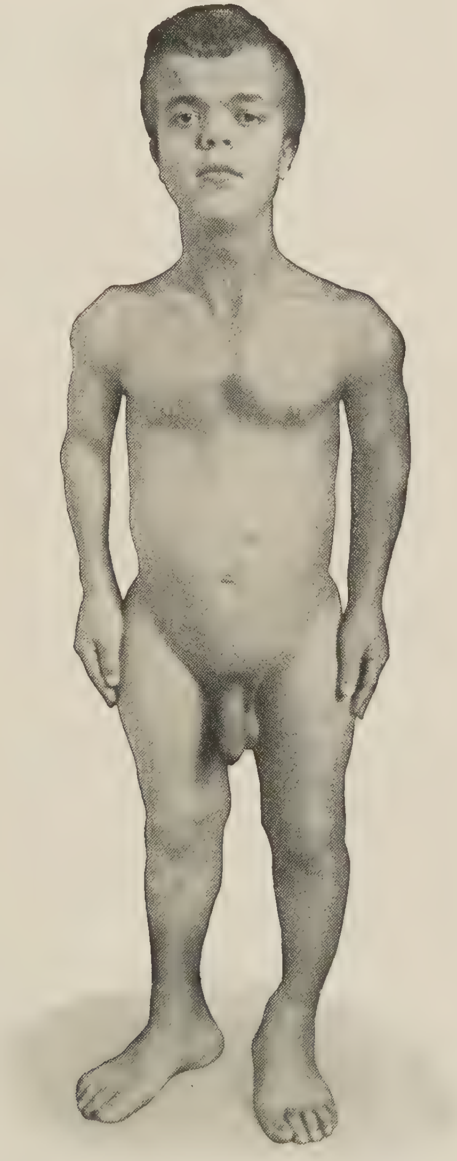

FIG. 87.—Chondrodystrophy (Observation LXIII).

There have also been described cases of partial chondrodystrophy. *Dufour* describes such a case, in which the upper extremities were hardly shortened, and also the trident form of the hands was not pronounced, while the lower extremities showed marked chondrodystrophic alterations. Especially noteworthy is the case of unilateral chondrodystrophy described by *Siegert* in his monograph.

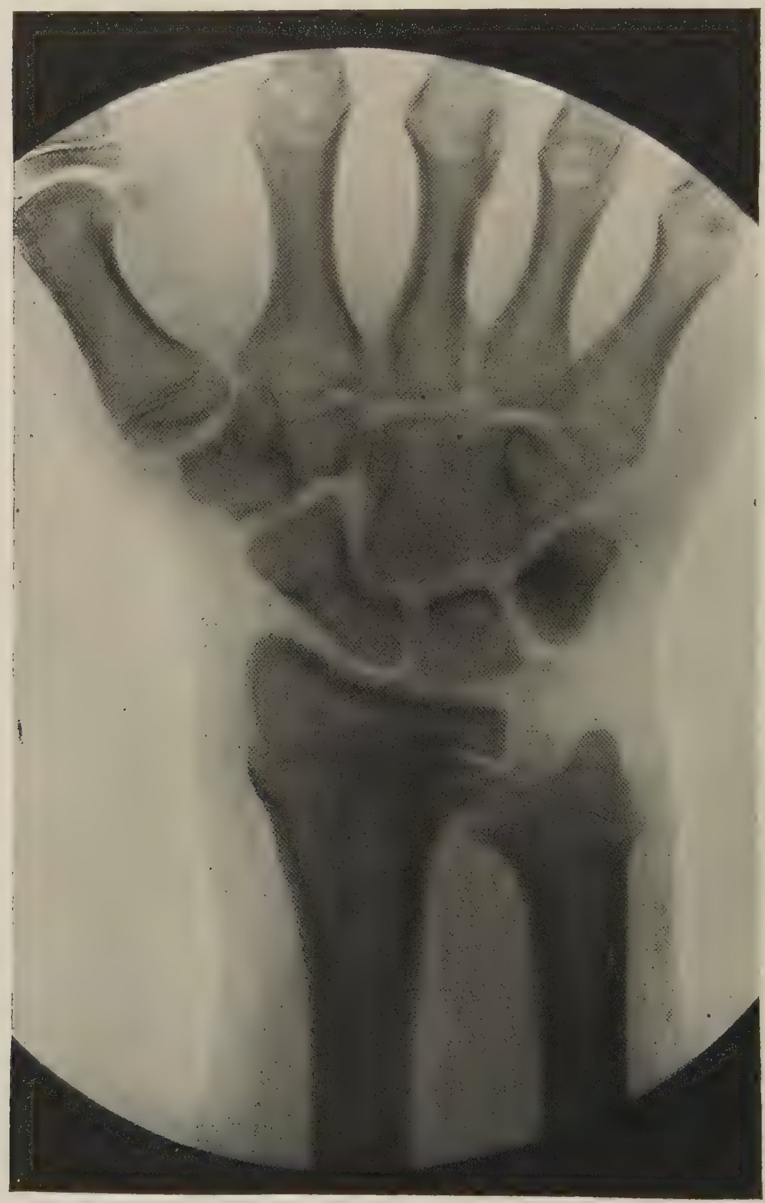

FIG. 88.—X-ray picture of the hand in chondrodystrophy (Observation LXIII).

The malacic form of chondrodystrophy is not capable of maintaining its life; both other forms may attain a high age. The aplastic form is recognizable by the absence of the vertebral and cranial synostoses described, and further by a characteristic position of the joints by which the extremities maintain a curved appearance (*Breus* and *Kolisko*). The dwarfs are for the most part especially small.

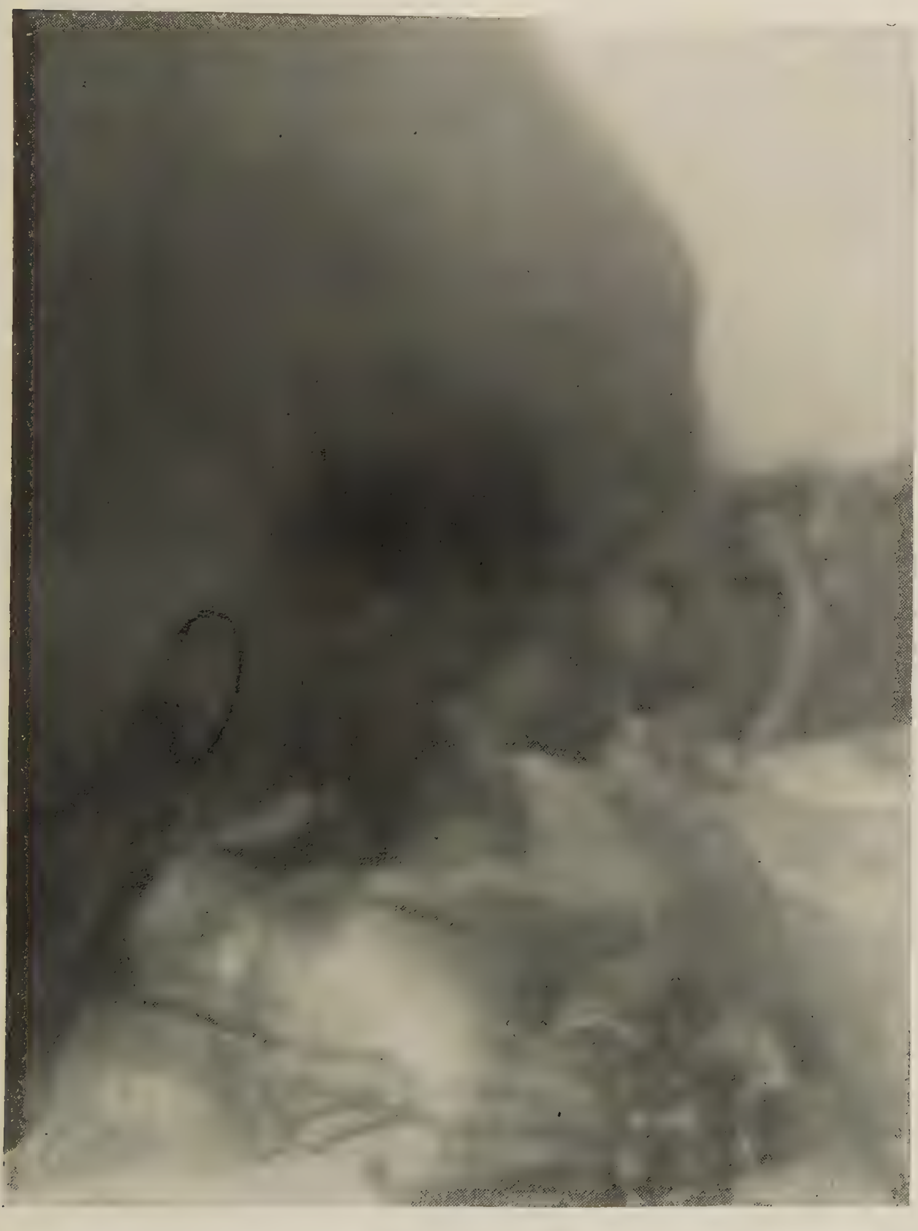

Fig. 89.—Sella turcica pressed flat in chondrodystrophy (retouched) (Observation LXIII).

For the characterization of the chondrodystrophic dwarf, it is also mentioned that they *all show a great family likeness* (*Porak*); that the gait in all is waddling, that the *intelligence develops normally, and that finally the sexual glands and the genitalia develop and functionate normally.* Indeed in many cases the genitalia are developed remarkably well.

Here are set forth two cases observed at the first medical clinic. The notes concerning the first case, four years old (Observation LXII), have unfortunately been mislaid. I can only show the characteristic illustration, that shows the characteristics of chondrodystrophic dwarf in pronounced manner. The root of the nose is markedly retracted; the extremities are enormously shortened, the skin has become too wide for its extremities, lying in thick folds.

*Observation LXIII.*—U. W., seventeen years old. Father of the patient normally developed. The same is true of the father's parents and three brothers and sisters (except that one sister has a syndactylism of three fingers). The mother of the patient seems to have had rickets in early life, but is of normal development. Of brothers and sisters of the patient only the youngest, a girl one year old, is living; she is entirely normal. The eldest child died at the age of fourteen years of tuberculosis, was normally developed. The second child died at three-fourth year, the third at one-fourth year, the fourth is the patient. The fifth and sixth died at one-fourth and one-half years, the seventh immediately after birth.

The patient, like the rest of the children, was according to statement normal at birth. At six months of age he seems to have had pain in passing urine, and soon after the father observed that the child remained behind in growth, and only the head was much too large. The increase in the size of the head lasted until about the seventh year. He learned to speak at two years, the intelligence developed entirely normally. At about one-half year he has had paresthesia and fatigue in the legs. He began to walk with knees pressed together and for some weeks sitting down has been difficult too.

Height 125 cm., span width 126 m., acromion to points of finger 47 cm.; upper border of trochanter major to the heel 53 cm. Length of hands, 15 cm., breadth 10 cm.; length of feet 21 cm.

The cranial skull is much larger than the facial skull, is somewhat quadrangular; root of nose deeply retracted. On looking to the left or upward, horizontal or vertical nystagmus respectively. *Chvostek's* phenomenon present on both sides. Slight dextroscoliosis of the thoracic spine. The hands are short and broad, the fingers alike in length, typical mains à trident. X-ray shows that the epiphysial junctures of the fingers are not as yet united. The sella turcica is pressed together in the vertical diameter, broadened in the horizontal.

The musculature is normally developed, the genitalia hyperplastic. There is no axillary hair, nor hair on the linea alba. There exists a moderately large struma of rather soft consistency.

There are spasms of the lower extremities. Legs adducted when at rest, with slight equinus position. Patellar and foot-clonus present, Babinski positive. Hypalgesia and hyperesthesia from about the height of the arch of the ribs downward, becoming less from the fossæ of the ilia down; very slight on the feet.

Summary. Typical Chondrodystrophy.—At first we thought of a hydrocephalus, descending degeneration of the pyramidal tracts and spastic paresis of the extremities. Yet there were no other points for our adhering to the diagnosis hydrocephalus. It is possible that the spastic paresis was produced by narrowing of the vertebral canal by the chondrodystrophic process. I refer to the case of *Lampe* mentioned above.

**Occurrence.**—Chondrodystrophy does not belong to exceedingly rare affections. According to *Katolicky* about 70 cases are known in adults. *Siegert* counts 53 females and 50 male cases. Several cases of familial or hereditary occurrence of chondrodystrophy are found reported in the literature. *Porak* mentioned a chondrodystrophic female dwarf who was delivered of a chondrodystrophic child through Cesarean section. *Porak* also cites a case of *Charpentier*, a twenty-three-year-old chondrodystrophic female dwarf, whose sister, father and great-grandfather had been chondrodystrophic dwarfs. *Poncet* and *Leriche* observed two chondrodystrophic sisters, *Decroly* saw chondrodystrophy in grandfather, father, and child. Also *Eichholtz* saw familial occurrence of chondrodystrophy. He saw two chondrodystrophic sisters, of whom one was a childless widow forty-two years old. The other, about forty years old, had an eighteen-year-old chondrodystrophic child. She was delivered through Cesarean section. Also the father of both women seems to have had chondrodystrophy. *Siegert* mentions that beyond these cases he could find no others of inheritance of the disease among the more than 100 cases reported in the literature. However, there are later observations. *Franchini* and *Zanasi* observed a chondrodystrophic man and wife. The woman became gravid and was delivered through Cesarean section. The child, which indeed the authors did not themselves see, was 80 cm. tall at the age of

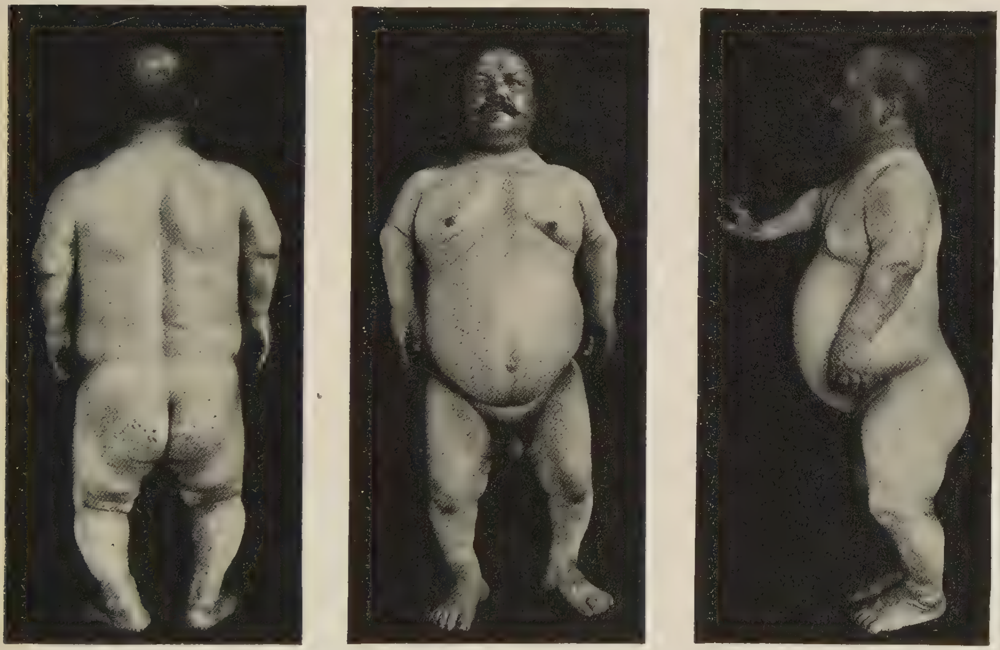

Fig. 90.—Chondrodystrophic family (Father—Observation LXIV).

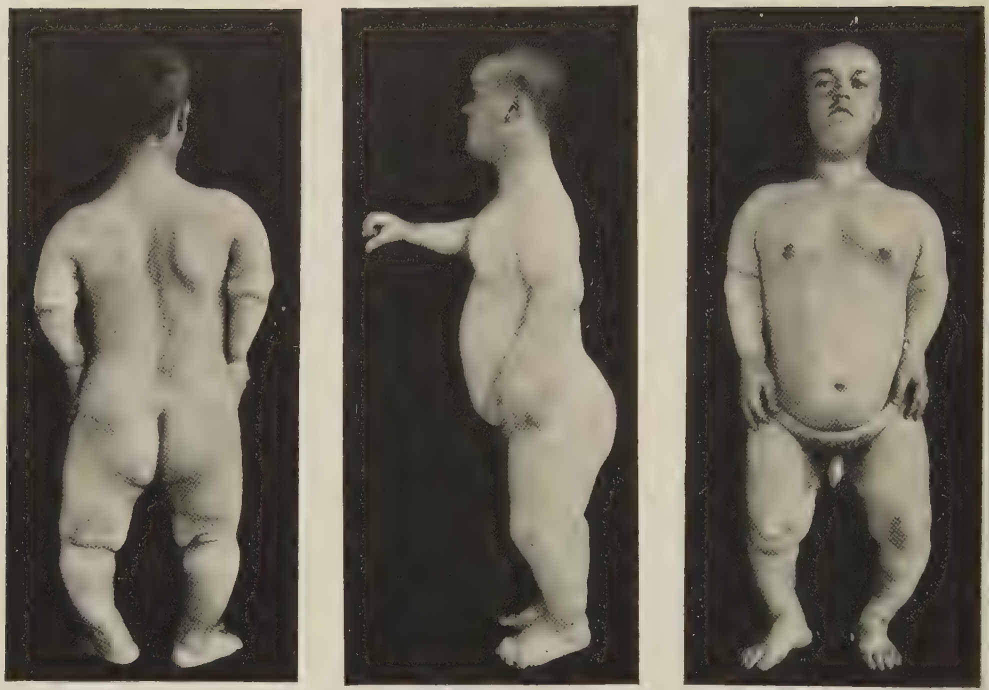

FIG. 91.

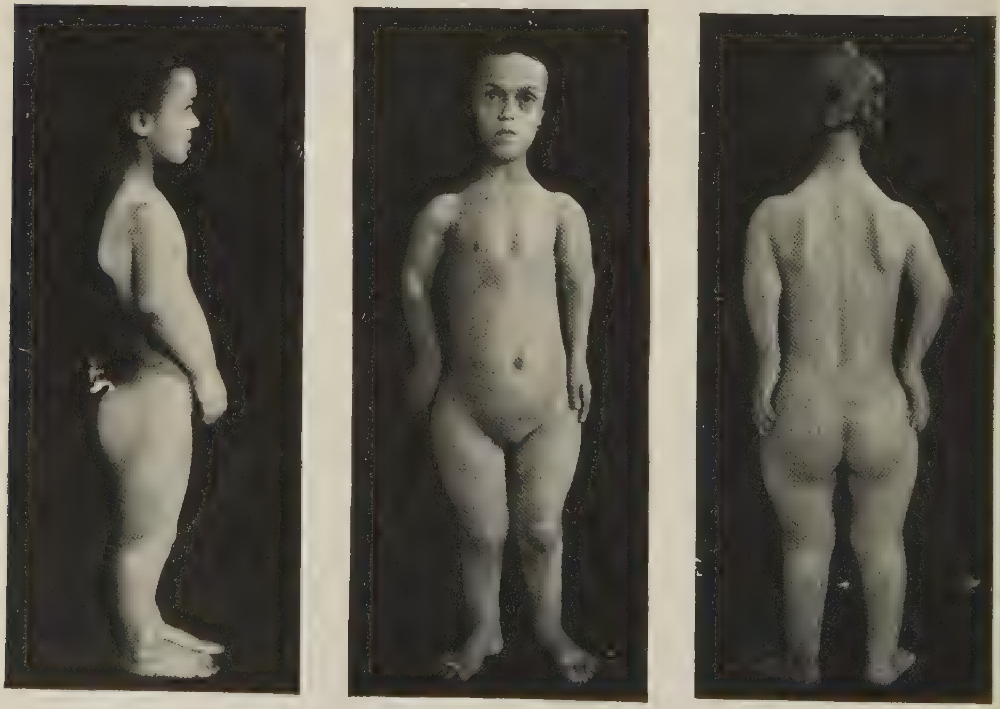

FIG. 92.

FIGS. 91 and 92.—Chondrodystrophic family (Son—Observation LXV and daughter—Observation LXVI).

twelve years, and had an enlarged head and shortened extremities. It seems thus also to have been a chondrodystrophy, as the authors suppose with entire correctness. *Glaessner* showed two cases of chondrodystrophy at the Wiener Gesselschaft der Ärzte. They were father and son, fifty-six and twenty years old, 101 and 108 cm. tall respectively. It was elicited that for four generations, dwarfism always existed in the male members of the family, while the women were entirely normal. A fine example of inheritance of the disease was also observed in the first medical clinic. It concerned a father, son, and daughter. I here reproduce the photographs. The father was forty-nine years old, the son nineteen, the daughter twelve years old. The wife of the father was of normal height. (Observation LXIV, LXV, and LXVI.)

**Etiology.**—As I already mentioned at the beginning chondrodystrophy was first regarded as fetal rickets, an assumption that was already the experiments of *Parrot* and *Porak* showed unfounded. *Virchow* regarded as typical for endemic cretinism the premature synostosis of the os tribasilaris that occurs in chondrodystrophy and on this supposition turned the attention to the thyroid gland in an etiological relation. The assumption of insufficiency of the thyroid gland is recognized as incorrect, as the results of the works of *Kaufmann* and later *Diederle*, in spite of which *Hertoghe*, *Stötzner* and *Moro* again adopted the thyrogenic origin of chondrodystrophy. In all accurately investigated cases the thyroid gland is entirely normal, however (*Diederle*, *Breus* and *Kolisko*, *Kassowitz*, etc.). The supposition of *Moro* that in his case there had occurred previously a dysplasia of the thyroid gland is not justified by anything. Also in the case reported by me, there was not a single symptom that belonged to the symptom-complex of hypothyrosis. As is known, also thyroid therapy is entirely without results, even in young individuals. Recently *Sumita* has set forth the untenability of thyroid-gland therapy.

*Lauze* points out that the buffoons of kings were chondrodystrophic dwarfs, who have been described as talented, loquacious, quick at repartee, "fond of everything that glitters," and sometimes also as maniacal. *Lauze* regards this mental condition as the result of hypersecretion of the interstitial glands. *Euzière* and *Delmas* describe a case of chondrodystrophy with psychical characteristics such as *Lauze* has described; they regard these however as an expression of degeneration and do not believe that such psychical earmarks stand in causal associationship with chondrodystrophy. In the cases of chondrodystrophy observed by me I could not observe any of the mental characteristics described by *Lauze*. The hypothesis of *Lauze* should hardly gain adherents.

**Differential Diagnosis.**—Nowadays we ought not to waste words considering the differential diagnosis from cretinism.

Another form of micromelic growth disturbance, *osteoporosis congenita*

(*Kundrat*) is characterized by a disturbance of the epiphysial as well as periosteal bone formation. Clinically, it has up to the present been without significance as the infants have never been capable of maintaining life; except that *Hagenbach* described a dwarf with tumor of the hypophysis, whose bone alterations *Hagenbach* regarded as osteoporosis. Up to the present there are no tenable relationships between this disease and the ductless glandular system.

## V. MONGOLISM

### (*Mongoloid Idiocy*)

Mongolism was first recognized as a disease sui generis by *Langdon-Down.* I shall here limit myself to a short delineation, paying especial attention to the differential diagnosis from infantile myxedema, in the course of which I follow the excellent descriptions of *Bourneville, Kassowitz, Scholtz* and *Siegert.*

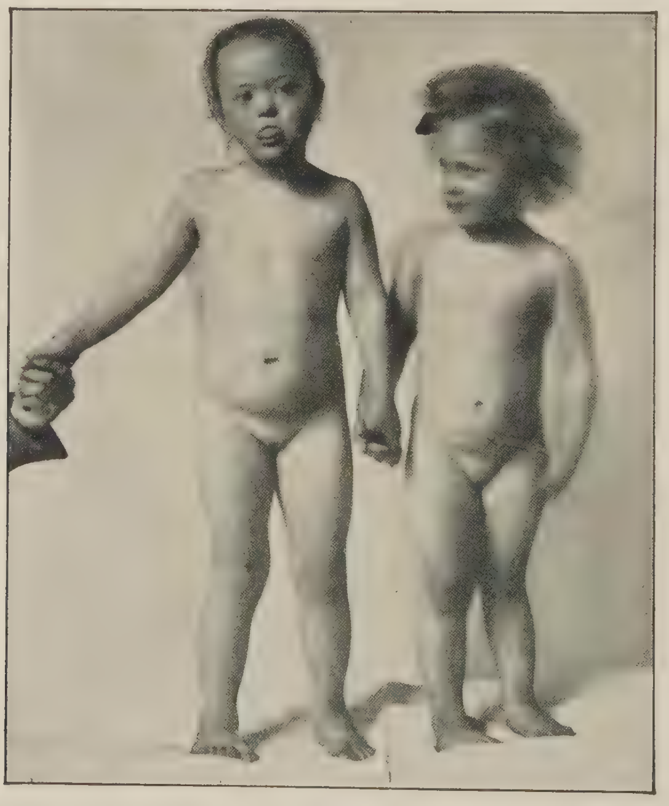

FIG. 93.—Six and one-half-year-old girl (Mongolism) with three-year-old healthy sister.

**Symptomatology.**—The Mongoloid children show a great family likeness. The term Mongolism is used because the physiognomy of these children shows great similarity to that of the Mongolian races. While in infantile myxedema the *skull* is mostly large and pronouncedly brachycephalic, in Mongolism it is *small* and *round*, the palpebral fissures are small and lack myxedematous swelling, they are placed oblique, are slit-like and show epicanthus; the nose is small and sits like a button on the broadened and somewhat sunken nose root (*Kassowitz*), while in infantile myxedema the root of the nose is strongly retracted, so that the nasal cavities become apparent. Mongoloids often show a conjunctivitis. The zygomatic arches protrude somewhat, the forehead is low and flat, the mouth is small but becomes broadened when the patient laughs, the *tongue* is not enlarged, or not essentially so, is fissured, is always somewhat between the separated rows of teeth, the lower jaw as a rule projects beyond the upper jaw. The palatal arches are high, the cephalic hairs are soft and silk-like, while in myxedema they are rough and dry and are here and there absent. The ears are small and stand back, the lobules have developed in the form of a triangle (oreille mongolienne), the facial expression is morose and unintelligent, in Mongolism it is vacant and expressionless only in the first years of life. Later it is gay, comical, imbecile. I refer to the accompanying illustration. The

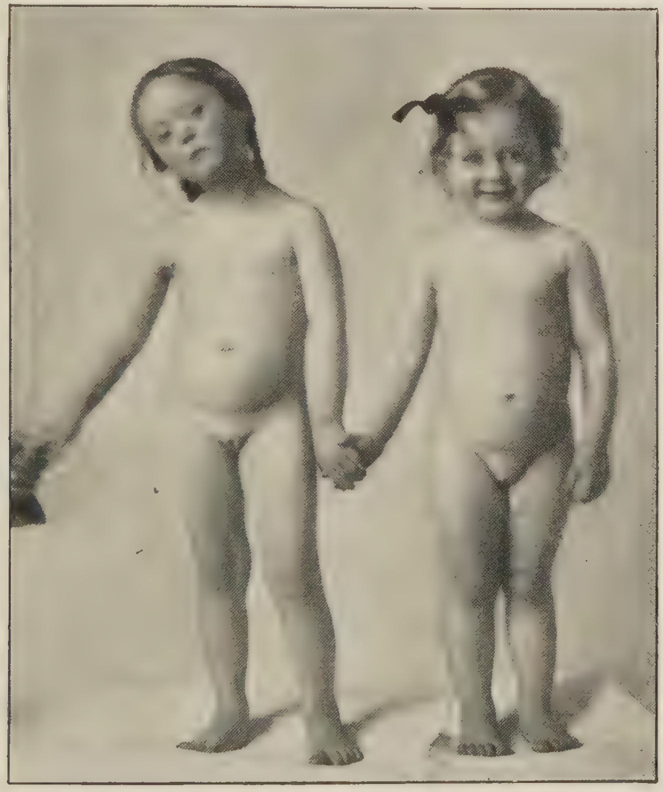

FIG. 94.—Same case after thyroid treatment.

cheeks lack the thickness of myxedema and usually show a macular redness. While in infantile myxedema or thyroaplasia the condition becomes recognizable only sometime after birth, Mongolism may be recognized immediately "c'est un petit chinois." The *fontanelles* and *sutures* are open abnormally long, *dentition* is somewhat delayed and somewhat irregular. The teeth are defective, and the set of teeth mostly shows numerous abnormalities. (Degenerationsgebiss-*Vogt*); growth in height is usually somewhat stunted, but there exists a difference from infantile myxedema in that all these manifestations are very much less pronounced, and the bone nuclei usually appear at the normal time or just a little later. In many a case only isolated bone nuclei appear late (*Vogt*). *Siegert* even observed premature ossification of the epiphysial nuclei. Later there often occurs a stunting of growth, and even a case of Mongoloid dwarfism has been observed by *Bourneville*. The *skin* is smooth and moist; the pseudolipomata of infantile myxedema are absent, and there often exists marked obesity. The neck is regular, not shortened as in infantile myxedema. The thyroid is present. Very commonly the *abdomen* is thickened, obstipation exists, and umbilical hernias are not rare. *Kassowitz* found umbilical hernias forty-four times among fifty-five cases, and three times a hernia in the linea alba below the umbilicus. Both the accompanying illustrations (Observation LXVII) for which I thank Dr. L. *Mohr* (Halle a. S) show the Mongolian expression of the face.

The skeleton is proportioned, slender, the children learn to sit and stand late, the hands are rather small, awkward, the middle phalanx of the little finger is often shortened, the end phalanx atrophic; also the thumb is often very short (main mongolienne). Very commonly the joints are extraordinarily low, especially the joints of the hands and feet, but also the hip-joints. The musculature is often hypotonic. Often other anomalies of formation occur, such as congenital cardiac defects, and not rarely slight strabismus or nystagmus. The genitalia are different from those of infantile myxedema, in that they remain only a little behind in development. In males, the penis and scrotum are often strikingly small, as *Kassowitz* found nineteen times in thirty-nine cases, and *Siegert* in half the cases. Also there may be delay in descent of the testicles. Later the genital functions are for the most part normal, although libido may be very slight. The Mongoloids are usually short-lived, and very sensitive to tuberculosis. The mental development is most only delayed, or there may be slight imbecility—and but rarely pronounced idiocy. The children are rather lively, but it is hard to fix their attention; they have considerable imitability and pose readily.

Hence there are very few features of infantile myxedema mixed in with Mongolism. These are eventually a slight degree of dwarfism, the delay of the dentition and closure of the fontanelles, the distention of the abdomen, the umbilical hernias, the constipation, the remaining behind in mental development, the anemia. There are, however, cases of Mongolism in which myxedematous symptoms are more prominent; *Vogt*, *Neurath*, and others have described such cases.

**Pathogenesis and Treatment.**—From what has been said, we should expect that thyroid-gland treatment would have only a slight influence. Sometimes not even acceleration of the dentition and closure of the fontanelles follow. Only the umbilical hernia and constipation are improved rapidly. *Kassowitz* says that in young children treatment with thyroid gland will only anticipate the improvement that later occurs spontaneously. In the case shown above, the results of its use may be regarded as extraordinarily good.

Although according to what has been said there tends to be present in cases of Mongolism a slight temporary athyrotic component, which may be more strongly pronounced in certain rare cases, yet there is no doubt that the clinical picture of this disease cannot be attributed to any disease of the thyroid. This is confirmed by the fact that in the few autopsies thus far recorded the thyroid for the most part was found to be normal (*Neumann*, *Comby*, *Bourneville*). Only *Phillippe* and *Oberthur* found in four cases sclerotic inflammation and *Lange* slight inflammatory changes. *Bourneville* in five cases, and *Siegert* in one case saw a persistent thymus. The findings in Mongolism do not present anything characteristic, and resemble those of idiocy (*Scholz*). *Kassowitz* considers the simultaneous affection of many ductless glands; which assumption lacks all objective evidence. Most worthy of remark in an etiological direction seems to me the oft repeated observation that Mongoloids are the last born in a family numerous in children, or that the mother was very old or her strength had been reduced through illness. *Shuttleworth* therefore terms the Mongoloids the "products of exhaustion."

In the *differential diagnosis* from infantile myxedema, the X-ray examination, in addition to the Mongoloid expression of the face, is of importance.

## Addendum

It is true that no term in medicine has been more abused than that of "infantilism," and that any special work done on the individuals affected with infantilism must be accepted with caution if the type of infantilism and exact description of the individual be not clearly stated. The author's attempt to delimit the affection is indeed very laudable; but it is true that the determination of the fine shades of distinction is often very difficult. Thus certain of the cases of pituitary tumor without apparent abnormal distribution of fat have been classed under the general term "infantilism." It is not at all certain that these cases would be included under any of the types mentioned by the author, although some do possess features that resemble closely the infantile types. Among these may be mentioned the type of "fat boy" described by *Cushing*, which *Cushing* regards as on the whole a hypopituitarism.

The various types of dwarfism present fairly well-defined characteristics.

*McKee*, who has had an extensive experience with Mongoloids, claims to have attained very good results from the use of thyroid-gland extracts.

### References

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## CHAPTER XIII

# THE DISEASES OF THE INSULAR APPARATUS OF THE PANCREAS AND THEIR RELATION TO DIABETES MELLITUS

A description of the pathology of the inner secretion of the pancreas offers beforehand many greater difficulties than that of other ductless glands, especially if the clinical manifestations are chiefly considered. The pancreas is not, like the other ductless glands, exclusively a gland with internal secretion. It belongs to the most important glands of external secretion; and anatomically shows chiefly the structure of one of these. Actually the physiology and pathology of the external secretion of the pancreas was for a long time the subject of investigation, before clinical observations, and then the experiments on the total extirpation of the pancreas led us to think of the possibility that the pancreas might have an internal as well as an external secretion.

**Historical Development.**—Already *Bouchardat* had observed sclerotic alterations of the pancreas in some cases of diabetes mellitus and on the ground of these observations had expressed the opinion that the cause of human diabetes depended on a disease of the pancreas. A secure experimental foundation for this view was first created by the celebrated experiments of *v. Mering* and *Minkowski.* These investigations showed that total extirpation of the pancreas in dogs, in addition to the disturbances of absorption due to the absence of the pancreatic juice, leads regularly to an excretion of sugar, indeed even to a severe, fatally ending diabetes.

First through this discovery was the interest of pathological anatomists generally turned toward the pancreas. In the course of the next decade there followed numerous statements as to various alterations of the pancreas in diabetes mellitus, sclerotic changes, inflammatory processes, etc.; yet in spite of the weight of the experimental finding, we could not overlook the fact that in many cases of severe diabetes mellitus the pancreas showed no demonstrable pathologico-anatomical alteration and that, on the other hand, in many cases of high-grade destruction of the pancreatic tissue, diabetes was entirely absent. The question assumed another aspect when attempts were made to bring the islands formerly described by *Langerhans* into relation with the inner secretion of the pancreas. While the glandular acini furnish the external secretion, the islands of *Langerhans* might constitute embryologically independent tissue element distributed throughout the entire pancreas, which might give off directly into the blood path a hormone important for carbohydrate metabolism. Especially important for this view was the observation of *Ssobolew* and of *Schulze*, that after ligation of the excretory duct of the pancreas, the acinous tissue gradually undergoes atrophy while the islands remain intact. Also the observations of the pathological anatomists show that the islands are much more refractory toward the action of various noxious agents than is the acinous tissue. This furnishes the explanation of the numerous cases of severe disease of the pancreas without glycosuria; on the other hand statements that in diabetes mellitus chiefly the islands diseased were constantly increasing, a direction that was first inaugurated by *Opie* and quite particularly upheld by *Weichselbaum*. Up to the present the insular theory has not, however, won general recognition, as it is found on the pathological anatomical side that there are constantly occurring cases in which in spite of an existing diabetes the insular tissue remains intact and even in certain cases, is especially well developed. This finding has led many authors to the view that both tissue elements of the pancreas, acinous and insular apparatus, produce the hormone. In recent years the problem of the internal secretion of the pancreas has experienced further complication; the view has been expressed that the significant influence that the pancreas exercises over digestion in the intestine depends not alone on the enzymatic properties of the intestinal juice but in part on the internal-secretory activity of the pancreas (*Lombroso*). Both tissue elements of the pancreas according to this are involved in both the external as well as the internal-secretory activities. This teaching has obviously caused much confusion.

Another aspect of the problem is the question *how* the pancreas takes part in the carbohydrate metabolism. *Claude Bernard* assumed that in diabetes there was increased sugar production. *Minowski* first expressed the opinion that on the absence of the pancreatic hormone the consumption of the sugar molecule in the body suffers harm. *Naunyn* inclines more to the view of a disturbance in glycogenesis (dyszoamylie). *Lüthje* first furnished the certain demonstration that in addition to the carbohydrates also the albumin is to be considered as a sugar builder. The increase in the sugar production has been more discussed again since the investigation of *O. Löwi*, *Eppinger*, *Falta*, and *Rudinger* assume in experimental pancreatic diabetes both reduction in the sugar consumption (removal of the specific internal secretion) as well as increase in the mobilization of sugar (consecutive increase of function of the chromaffin tissue) a view that *I* promulgated for human diabetes. On the ground of the investigations of *Porges* and *Salomon*, *v. Noorden* brought the increased sugar production again into the foreground, while lately *Starling* and *Knouthon* have advocated the exclusive disturbance of sugar combustion.

As to what finally is the significance of the pancreas for the pathogenesis of human diabetes views diverge greatly. The discovery of sugar puncture by *Claude Bernard* led to the viewing of each case of diabetes as neurogenic. After the discovery of experimental pancreatic diabetes, attention was drawn on the contrary to the pancreas. Of course between the experimental pancreatic diabetes and the genuine human diabetes there exist considerable differences. The intensity of the glycosuria is much higher in the latter. In association with *Grote* and *Staehelin*, *I* have pointed to the enormous increase in the decomposition of albumin and the respiratory exchange of gases in experimental pancreatic diabetes. In genuine human diabetes on the other hand the demand for albumin as well as the demand for calories is not increased. The supposition of *Benedict* and *Joslin* that the heat production in human diabetes is increased I cannot subscribe to, the reason for which I shall detail later. In consideration of these essential differences *I* have taken position as regards the pathogenesis of human diabetes in a direction contrary to the pancreatocentric; as also *v. Noorden*, on the ground of his clinical experience and the investigations carried out in his clinic, has upheld the view that in addition to the pancreas, a high value must be ascribed to the chromaffin tissue or the nervous system.

In addition to the pancreas and the chromaffin tissue, the thyroid gland is certainly of importance in the genesis of many diabetic glycosurias.

The *manner of procedure* in the following dissertations must, in order to render possible a condensed exposition of the manifold and complex questions deviate in some points the scheme followed thus far. After some introductory remarks as to the anatomy and embryology of the pancreas the results of the experimental investigation will be given more space than has hitherto been the case. Especially will I treat in detail the metabolic disturbances that occur in animals after total extirpation of the pancreas. Also experimental nervous diabetes, so far as it has not already been considered in the chapter on the suprarenals, will be dwelt on. In the clinical part, I shall first describe the gross anatomical disturbances of the pancreas simultaneously with the accompanying alterations of metabolism. Then will follow a short exposition of the clinical manifestations of genuine diabetes as far as this is necessary in order to emphasize the points of difference from the changes in metabolism in experimental pancreatic diabetes. On the contrary the pathological anatomy of genuine diabetes mellitus will be treated more in detail, wherewith the alterations of the pancreas, as well as that of the central nervous system will be considered. Only then will I enter into the question as to what rôle the inner secretion of the pancreas, or the pathologico-anatomical alterations of the insular apparatus play in the pathogenesis of diabetes mellitus.

**Anatomy and Embryology.**—The pancreas is a long-drawn-out cylindrical organ situated behind the stomach just in front of the pars lumbalis of the diaphragm. We distinguish from right to left, the broad head lodged in the loop of the duodenum, the neck, the body, and the tail. The head is intimately adherent to the loop of the duodenum, while the left end (processus uncinatus) is more movable. On its anterior surface, the pancreas is covered with peritoneum. The length of the organ is about 19–22 cm., the weight, according to *Vierordt* varies between 85 gm. and 105 gm., according to *Orth* between 90 gm. and 120 gm. The pancreas is extraordinarily well vascularized. It receives a large branch (arteria pancreatico-duodenalis superior) from the ramus gastroduodenalis of the hepatic artery, further several branches from the splenic artery, and one branch (arteria pancreatico-duodenalis inferior) from the superior mesenteric artery. The pancreas is supplied by an abundant nerve plexus, of branches from the vagus and from the sympathetic fibers that emanate from the sympathetic trunks or from the great sympathetic ganglia.

The glandular acini of the pancreas form large lobes bound together by loose connective tissue that are in turn made up of smaller lobules. The excretory ducts of the acini unite in the pancreatic duct or duct of Wirsung, that empties in common with the ductus choledochus into the papilla of Vater in the duodenum. A large excretory ductus pancreaticus accessorius, emanating from the head, unites with the duct of Wirsung. From the accessory duct there usually branches a duct uniting with the duodenum (ductus Santorini). *Opie* found this duct obliterated or markedly narrowed in numerous cases. Only in such cases was the secretion of the pancreas fully cut off from the intestine by closure of the principal duct. The closure of the accessory duct may lead to isolated sclerosis of the head of the pancreas. Further, we should consider that not infrequently accessory lobules of the pancreas are found in the duodenum.

In the lobules of the glandular parenchyma are found imbedded between the individual acini cell groups that consist in polygonal cells with large round nuclei. These cells stain less distinctly than the cells of the acini. The protoplasm is lighter, it does not show the distinct zymogen-granules as does the glandular tissue. These cell groups, which occur in very different number and size, are named after their discoverer, the islands of *Langerhans*. They are found in all kinds of animals (*Diamare*), and in some they are very large and even visible microscopically. They show an especial abundance of blood-vessels. The capillaries form a dense network interlarding the cell groups similar to what we see in the renal glomerules (*Kühne* and *Lea*). The cell accumulations have no connection with the excretory ducts of the gland. They are never filled after the injection of the excretory ducts (*v. Ebner*). Many histologists state that the islands of *Langerhans* are surrounded by a capsule (*Renaut, Opie, Flint*, and *others*). Others combat the existence of a capsule (*Diamare, Hansemann*, and *others*). At any rate it should be mentioned that in many species of animals (for example in the cartilaginous fishes) the capsules are found constantly (*Rennie*).

Very different views have been expressed as to the nature of these pictures. *Langerhans* regarded them as nervous structures, later authors as lymph follicles. Finally the view was promulgated that they constitute a gland with internal secretion distributed throughout the entire pancreas, that gives off an internal secretion to the interlarding capillary network.

According to the views of these authors the islands of *Langerhans* are completely independent. On the other hand authors state that the insular tissue may shade off into the glandular tissue and vice versa. *Laguesse* first described intermediary forms between the gland cells and the island cells, and assumed that on certain functional demands there was a transition from the one kind of tissue into the other (*balancément*). *Karakascheff* is of the opinion that the islands constitute only a sort of reserve material, and that under certain conditions, for example in the giving-out of gland tissue there enters into play a regeneration of the parenchyma from the islands. On the other hand, *Gutmann* would see a changing of the parenchyma into insular tissue. Also *Swale Vincent* and *Thompson* suppose transitions between the gland cells and the island cells. The recent embryological studies and investigations as to the regeneration processes in the pancreas do not seem to confirm the opinion of these authors.

The pancreas is of entodermal origin. There are present three rudiments, a dorsal, made up of the epithelium of the primitive duodenum, and two ventral proceeding from the groove-shaped rudiment of the ductus choledochus. *Laguesse* first showed that the islands as well as the glandular parenchyma is of epithelial origin, and also showed that the islands separate out from the primitive cell columns at the same time as the glandular tissue. The newer investigations on human fetuses (*Pearce*, *Weichselbaum* and *Kyrle*, *Mironescu*) leave room for no doubt that the island tissue already in earliest fetal life develops from the epithelial cell columns just as do the acini.

The youngest fetus in which the islands of *Langerhans* were observed was 54 mm. long (*Pearce*). *Weichselbaum* and *Kyrle* did not find them present as yet in a fetus 50 mm. long. The islands are first found in the distal part of the pancreas. Also in adults they are more frequent in the tail of the pancreas (*Opie*). *v. Hansemann* assumed that the islands were of mesenchymal origin, but *Weichselbaum* and *Kyrle* found them also later still in association with the excretory duct of the pancreas, and hence regarded them as entodermal. Further, also the observations as to the regenerative processes in the pancreas after abundant destruction of glandular tissue show that the islands always develop from the excretory duct (*Ssobolew*, *Kyrle*); especially beautifully do the investigations of *Kyrle* show that on implantation of pieces of pancreas into the spleen, in the regenerative processes that soon make their appearance, the island and acinous tissue develop independently out of the epithelium of the excretory duct.

## I. EXPERIMENTAL PART

### A. Diabetes after Extirpation of the Pancreas

We shall first describe *carbohydrate metabolism* after extirpation of the pancreas. The complete extirpation of the pancreas causes in all kinds of animals disturbances in the metabolism of sugar. It is true that in certain species of birds this does not go as far as glycosuria, but there results a hyperglycemia. The significance of the pancreas for the metabolism of sugars is therefore universal. The extirpation of the organ in dogs has been studied the most exactly; I shall therefore make especially the observations in the experiments on dogs the foundation of the following dissertation. The complete removal of the pancreas in dogs always causes a diabetes. The negative results that were obtained by certain investigators, especially those who preceded *Mering* and *Minkowski*, are referred to the fact that total extirpation of the pancreas is very difficult and sometimes slight remnants suffice to prevent the outbreak of the disease. *Lüthje* has contributed still later reports in which in spite of complete extirpation, the glycosuria remained absent. There occurred however as *Lüthje* himself stated, hyperglycemia after the operation, and later histological examinations of the duodenum showed that remnants of pancreatic tissue were present. In more than forty experiments that we ourselves have instituted in the course of the last year, like *Minkowski* we never missed the occurrence of a severe diabetes. When about a third of the organ is left behind, diabetes usually remains absent, but can, however, develop later if the piece left behind undergoes inflammatory processes. If a still smaller piece of the pancreas is left behind, there occurs a light diabetes, that is, excretion of sugar occurs only when the carbohydrate metabolism is overstrained by the administration of a diet rich in amylaceous material (*Sandmeyer's* diabetes).

The sugar that is excreted in the urine after the total extirpation of the pancreas is grape-sugar. The sugar elimination usually starts only a few hours after the operation and in about forty-eight hours the diabetes is at its height. Before the death of the animal the excretion of sugar usually gradually sinks. The duration of life after the operation is at the most fourteen days. Exact information as to the intensity of the excretion of sugar is furnished by the excellent work of *Minkowski*. This author showed that administration of sugar raises the existing glycosuria by the amount administered, and further that at the height of the disturbance in metabolism the amount of excreted sugar bears a definite relation to the amount of excreted nitrogen. This quotient, D:N, remains 2.8 to 3 [: 1], just as well when the dog is fasting as when it is fed with meat or other albuminous body. *Minkowski* hence drew the conclusion that in this quotient is expressed the extent to which the animal organism is enabled to form sugar out of albumin. The animals become poor in glycogen extraordinarily rapidly. After forty-eight hours the liver is almost free of glycogen and later becomes highly fatty. The glycogen is retained in the muscles for a long time, however. Even the leucocytes are strikingly rich in glycogen. Administration of grape-sugar cannot halt the disappearance of glycogen. The power of forming glycogen does not however disappear entirely, for on the administration of levulose a part of the same may be deposited as glycogen, in which case, as *Eppinger* and *I* observed, also the fattening of the liver is halted. A part of the levulose is excreted as levulose, another portion as glucose. The question as to whether the increase in elimination of sugar conditioned by the administration of albumin, depends on the direct formation of sugar from albumin was discussed very energetically, especially through the numerous objections of *Pflüger*, until *Lüthje* ascertained that after abundant administration of casein the total amount of the excreted sugar far exceeds the possible amount of stored glycogen. The administration of fat does not increase the excretion of sugar, yet it is to be considered that as a result of the absence of pancreatic juice, fat is very poorly absorbed. On the simultaneous administration of pancreatin we have, however, seen in individual experiments appreciable, although only transitory increase in the D : N quotient (to 7).

In addition to the glycosuria there exists polyuria and ketonuria. The occurrence of the latter is combated by many authors, although the experiments of *Embden* and *Lattes* let it be expected that in the pancreas-diabetic dog there exists a predisposition to ketonuria. If the blood of normal cattle was allowed to flow through the liver of a pancreasless dog, there was found as great an amount of diacetic acid as the liver of normal animals lets be produced only on the addition of the strongest acetone formers. *Allard* saw in addition to this, in pancreasless dogs, the occurrence of a not inappreciable amount of diacetic acid and betaoxybutyric acid especially when pieces of pancreas were placed under the skin of the abdomen and only later extirpated; when therefore the development of the diabetic disturbance of metabolism was retarded. In such animals ketonuria then develops rather rapidly and eventually leads also to coma.

Also the albumin metabolism in pancreatic diabetes shows definite disturbances. Already *Minkowski* had shown that after removal of the pancreas there occurs an increase of the albumin decomposition. In collaboration with *Grote* and *Staehelin*, *I* showed that this increase is constant and its intensity conformable to law. The hunger albumin exchange after complete extirpation attains to three or three and a half times the hunger albumin exchange before the extirpation. *Mohr* found less values; however, *Eppinger*, *Rudinger*, and *I*, in the later investigations confirmed our former statements.

Also the excretion of salt is appreciably increased, according to the investigations of *Whitney* and *myself*.

Finally the respiratory metabolism is essentially increased, according to the investigations of *Grote*, *Staehelin* and *me*, and of *Mohr*. Our investigations were carried out in *Jaquet's* respiratory apparatus. Already the appreciable increase of the albumin destruction would lead one to expect an increase of the caloric production, on account of the specific dynamic energy of albumin. According to our investigations, however, the increase of the exchange (about 42 per cent. in the experiments not complicated with fever) was higher than could be calculated from the destruction of albumin. An increased exchange might be anticipated also from the rapid losses of body weight, such as were ascertained in the later experiments I carried out with *Eppinger* and *Rudinger*.

For the reason that bodies very rich in oxygen (sugar and ketone bodies) are excreted, the respiratory quotient is very low. In our experiments it averaged about 0.73.

In the pancreasless dog the excitability of certain sympathetic nerves is increased. *O. Löwi* showed that the instillation of atropine into the eye of a pancreasless dog would produce mydriasis, a stimulus that had been below the threshold thus becoming operative. With this agrees the fact that subcutaneous or subperitoneal injection of adrenalin, increases, according to *Eppinger*, *Rudinger* and *my* experiments the D:N quotient. The amounts of sugar that raised the quotient to more than 2.8 were greater than those which under like conditions could be obtained by the injection of adrenalin into normal fasting dogs. Therefore the glycosuric action of adrenalin in pancreasless dogs is increased. As these experiments with adrenalin were undertaken at the height of the metabolic disturbance, therefore at a time when the glycogen constituent was already reduced to a minimal, it may be supposed that this increase is brought about not only by the increased consumption of glycogen, or through a washing-out of circulating sugar, but also through an increased formation of sugar.

Also *other* ductless glands influence the intensity of the pancreatic diabetes. The experiments on simultaneous extirpation of the thyroid gland or the parathyroid glands [together with the pancreas] show this. It is known that after thyroid extirpation the hunger albumin exchange is lowered. When the pancreas is simultaneously extirpated the hunger albumin exchange is about three to three and one-half times that of a thyroidectomized dog the same size, is therefore absolutely lower than after extirpation of the pancreas alone. The excretion of sugar is, however, the same, so that the quotient of dextrose to nitrogen (D : N) is higher. In experiments in which, together with the pancreas, a large part of the parathyroid glands was extirpated, we found further that the intensity of the diabetes was essentially increased. We observed quotients of 3.6, although the hunger albumin destruction (in relation to the body weight) was greater than was to have been expected in dogs of the same size after extirpation of the pancreas alone. Further, worthy of mention as the statement of *Zülzer* that in an experiment on a dog in which the pancreas was extirpated and simultaneously the renal vein was ligated, the intensity of the excretion of sugar was very slight and transitory.

We shall now enter further into the question as to *how* we may explain the occurrence of glycosuria after extirpation of the pancreas, or the *regulatory influence of the pancreas* on sugar metabolism under normal relations. It is generally recognized that in the present state of our knowledge, the assumption of an internal secretion of the pancreas is not to be avoided. Opinions of former authors, that the irritation or injuries to the sympathetic nerve plexuses in the course of the severe operations determined the glycosuria, are contradicted by the transplantation experiments of *Minkowski* and *Hedon*. If the part of the pancreas lying in the mesentery of the duodenum is transplanted with its vascular peduncle, under the skin, and later the rest of the pancreas removed, diabetes does not occur. A minimal [operative] attack then suffices to remove the transplanted piece and to call forth a diabetes in its fullest intensity. That the presence of pancreatic juice in the intestine is not necessary for the normal course of the carbohydrate metabolism is readily seen in the fact that administration of pancreatin essentially improves the absorptive disturbances, but rather increases the intensity of the excretion of sugar.

The experiments detailed lead us to assume, as already mentioned, an inner secretion of the pancreas. We have not as yet succeeded, however, in isolating the internal secretion and defining it chemically. We are not even certain as to the path of the giving off of the same. *Biedl* showed in his interesting experiments on dogs that after leading off the lymph of the thoracic duct to the exterior, glycosuria can occur. *Biedl* concluded from that the inner secretion of the pancreas is carried off by the lymph. Later *Biedl* and *Offer* stated that adrenalin glycosuria can be prevented by the simultaneous injection of duct lymph. If the internal secretion of the pancreas were carried off by the lymph we would expect that on the administration of the lymph of normal dogs to pancreasless dogs the intensity of the metabolic disturbances would be essentially reduced, or that the excretion of sugar would completely disappear, at least for some time. In numerous investigations as to this point we could not find these things. In large dogs that were fed abundantly with carbohydrates, the lymph from the thoracic duct was collected for some hours, and this lymph administered to pancreasless dogs either subcutaneously or by the drop-by-drop method into an exposed vein, without producing an essential influence on the quotient of dextrose to nitrogen (D : N), although for hours only. When *Biedl* more recently states that he succeeded in similar experiments to depress the D : N ratio from 1.8 per cent. to 1.5–1.2 per cent., it seems to me that the difference is much too small to decide as to this important question. Recently an attempt has been made by *Tuckett* to explain the glycosuria occurring in dogs with a lymph fistula through the operative injury to the sympathetic nerve in the neck and also through the narcosis. This explanation it seems to me, in consideration of the high percentage of sugar found by *Biedl*, does not appear satisfactory. If the internal secretion of pancreas is not carried off by the lymphatics—I leave this question open—there remains its transference by the pancreatic veins.

We have for this reason collected the blood of the pancreatic veins of large dogs and injected subcutaneously the serum of pancreasless dogs. Also in these experiments were the results negative. *V. Ehrmann* has carried out the same sort of experiments with similar negative results. Not much can be concluded from these experiments. The pancreas is extraordinarily well vascularized; it may be that the amount of blood collected in a half hour does not contain enough internal secretion to produce distinct evidence. It should also be considered that under normal relations the blood of the pancreatic vein is carried directly to the liver, whereas in our experiments it entered directly into the greater circulation. Finally we should consider the possibility that the internal secretion is bound in the blood corpuscles. The excellent vascularization of the pancreas may also furnish the foundation for the fact that we have not as yet succeeded in obtaining an extract of the pancreas that is active in influencing metabolism. The relations here seem to be similar to those affecting the likewise well-vascularized parathyroid glands. The pancreas is also in respect to its internal secretion no storage gland as, for example, the thyroid is. Probably the internal secretion is carried off as it is formed. *Zülzer*, acting on similar considerations, has ligated the veins of the pancreas, thus producing a stasis, and claims to have seen a favorable influence of the extract obtained from such a gland on the glycosuria of pancreasless dogs and on the ketonuria of human diabetes. It is true that the statements of *Zülzer* are not very convincing. The results in pancreasless dogs are very slight, and on the injection of the extracts into human beings shiverings are produced that influence the metabolism in a non-negligible way.

The question as to which tissue element of the pancreas is to be referred, the production of the hypothetical internal secretion has, since the discovery of the islands, been much discussed, especially with respect to human diabetes. I regard it as suitable to consider quite separately the results obtained in animal experimentation, as much speaks for the assumption that human diabetes is not of a single nature and as the disturbances of absorption, observed after shutting-off of the pancreatic juice in the animals experimented on seem to deviate in many respects from those in man. Soon after the discovery of Langerhans' islands the view was expressed that these pictures, which in their histological structure show a certain similarity to certain ductless glands, especially the suprarenal cortex and the parathyroids, produce the internal secretion of the pancreas while the glandular parenchyma is concerned exclusively with the production of the external secretion. The view that was later upheld by several authors, namely, that the Langerhans' islands could pass over into glandular parenchyma, or reversely; I have mentioned this in speaking of the anatomy and embryology of the pancreas; in which exposition, in consideration of all the data as to the histological and embryological observations, I have accepted the views of those authors who ascribe to the insular apparatus a morphological and embryological independence. Of especial importance for the insular theory, were, more recently, *experiments that make a functional independence in high degree possible.*

Already *Katz* and *Winkler* had made the observation that after ligation of a larger excretory duct the islands last for a while, while the glandular parenchyma in the part of the pancreas affected goes to pieces. The general attention was first however attracted to this subject by the mutually independent observations of *v. Ssobolew* and *Schulze. Schulze* ligated in guinea-pigs a large lobe of the pancreas and found that even after eighty days the islands were retained, while in the sclerotic tissue were found only traces of the acini. It further should be mentioned that according to *Schulze's* investigation the islands undergo no alteration during fasting, while the pancreatic acini show alterations conditioned by the reduced function. *Schulze* came to the conclusion that the islands are entirely independent structures. *Ssobolew* experimented in rabbits, cats, and dogs. The results in rabbits were the clearest. The pancreas in rabbits, which lies flattened-out between the two layers of the mesentery possesses one excretory duct only. When this is ligated the pancreas shrinks markedly, owing to atrophy of the glandular parenchyma. It is true that *Ssobolew* found, between the thirtieth and the one hundred and twentieth day after the operation, slight sclerotic alterations of the islands in their clump of sclerotic tissue, but later the islands partially recovered; and they were retained even four hundred days after the operation. They also survived after analogous operations in dogs and cats. In dogs, *Ssobolew* found the atrophy of the glandular tissue less marked, as he supposes that it forms new excretory ducts. *Tiberti* found, after ligation of the excretory duct in rabbits, at first increased formation of zymogen-granules in the acini, that he regarded as hypersecretion, then hyposecretion, and finally complete cessation of granule formation. Later slight regeneration of the excretory duct made its appearance. In later investigations *Tiberti* found that the greater part of the acini disappeared, and that pictures remain behind whose significance as remaining islands is not clear. In two rabbits, *Tiberti* found slight glycosuria five months after the operation. In dogs, according to *Tiberti's* investigations, the sclerosis of the pancreas is less distinct than in rabbits, as islands as well as acini are in part retained.

*Visentini* ligated the excretory ducts of the pancreas in twenty-four dogs; he examined the pancreas two hundred and twelve days after the operation and found a gradually progressing sclerosis. Even one hundred and twenty days after the operation were found individual gland-lobules; in two experiments after two hundred and sixty and two hundred and twelve days (respectively) the glandular tissue had entirely gone to pieces. In the dog that survived two hundred and twelve days there was found a slight glycosuria.

*Sauerbeck* found after ligation of the excretory duct in rabbits gradually progressing sclerosis of the glandular parenchyma, the islands, similarly as in the investigations of *Ssobolew* showed transitory damages to its structure, owing to the sclerosing process. In this stage, *Sauerbeck,* in agreement with the older experiments of *Hedon* often observed glycosuria, sometimes considerable; in later stages the islands again showed their normal structure, and then no glycosuria existed. *Lombroso* found in forty-one pancreases of dogs that the ligation of the pancreatic duct did not lead unconditionally to sclerosis. Islands as well as acini could be in part retained.

In ligation of the duct in rabbits, *Lombroso* and *Sacerdote* found that the islands were indeed retained, but that their number and size were diminished.

Finally should be mentioned the investigations of *Zuntz* and *Mayer.* After ligation of the excretory duct of the pancreas, these authors found abundant retention of gland-acini in certain cases, showing more or less alterations of their structure. Very exceptionally indeed did the acini seem to have changed their structure. The islands of *Langerhans* likewise showed alterations of structure "perhaps they seem smaller, but their number does not seem to have been diminished." A portion of the island cells showed alterations even already after a few days; in every case the alterations of the islands developed much more slowly than those of the acini.

*Lombroso* in his works and in a detailed review has subjected to criticism the experiments just referred to, and has come to the conclusion that the functional independence of the islands of *Langerhans* has not as yet been demonstrated. In this conclusion *Lombroso's own views* that to the external secretion of the pancreas must not be ascribed that freedom and independence of the internal secretion that we for a long time tended to ascribe to it, has had a great influence. Before I discuss the question of the independence of the insular apparatus, I must enter first into an account of the disturbances of absorption after extirpation of the pancreas or after ligation of its duct.

Already *Abelmann,* whom we have to thank for the fundamental absorption experiments after extirpation of the pancreas, stated that it is true after total extirpation, the absorption of fat in the intestine almost completely ceases, although fat-splitting may be very good; that, however, the disturbance of absorption never reaches to this extreme grade when a part of the pancreas is left behind, even when its connection with the intestine is entirely broken up. Also after ligation of the excretory duct is the disturbance of absorption never intense. It has been attempted to explain this by the statement that in this case the pancreatic juice is in part absorbed, and reaches the intestine by way of the blood-vessels or that the dogs with pancreatic fistula lapped up the secretion that flowed out. (*Sinn, Hess, Burckhardt, et al.*)

Besides this it is mentioned that in dogs there often occur accessory pancreases, and that in such cases therefore the complete cutting-off of the pancreatic juice from the intestine is very difficult. *Sinn* and *Hess* found almost regularly in dogs a third excretory duct of the pancreas. According to these authors the ligation of all ducts is especially difficult intra vitam. When it really succeeds, there occurs within some weeks an almost complete necrosis of the pancreatic tissue. In these cases *Hess* and *Sinn* found no diabetes, in most cases however an appreciable temporary disturbance of albumin and fat absorption. In some cases indeed the absorption was quite good. *Lombroso* in his numerous experiments has ascertained the following: The absorption of fat in dogs is rather good when the entire number of ducts are ligated, or when after a part of the pancreas has been transplanted and a fistula from this to the outside has been made, the other part of the pancreas has been extirpated. This also occurred, according to *Lombroso,* when the re-ingestion of the secretion was entirely prevented.

In an experiment carried out in *Minkowski's* laboratory the disturbance of the absorption of fat was indeed not inappreciable (up to 60 per cent.). When later the vascular nervous pedicle of the transplanted part of the pancreas was ligated and cut, a transitory glycosuria occurred, and the fistula secreted further. Only after extirpation of the remaining part of the pancreas did the diabetes and the disturbance in fat absorption reach its full height. In a second analogous experiment, glycosuria was present from the first, but the disturbance of absorption in this case was less (38.7 per cent.). *Lombroso* further showed that bile, saliva, and intestinal juice show no alterations in their enzymatic characteristics, and that therefore an excretion of absorbed pancreatic juice into the intestine was therefore improbable. This was also confirmed by *Zuntz* and *Mayer. Lombroso* concluded from his experiments that the influence of the pancreas on the absorption of fat was also conditioned through an internal secretion. *Fleckseder* has instituted analogous experiments. Also he observed that the using up of fat and albumin is somewhat diminished in the fistula animals, whether the secretion is let flow free from the fistula, or is let stagnate, whether it is re-ingested or not. Very interesting is an experiment of *Fleckseder's* in which gradually, through increasing sclerosis of the piece of pancreas left behind, a diabetes developed to full height, the secretion from the fistula stopped, but the absorption of fat was, however, better than before.

*Lombroso* in his review has, as before mentioned, doubted the significance of the ligation experiments for the functional independence of the pancreas. He uses the just mentioned disturbances of absorption in a like sense, and comes to the conclusion that islands as well as gland parenchyma take part in the production of the external secretion of the pancreas, and that this is of importance for the carbohydrate metabolism as well as for fat absorption.

The amalgamation of both questions seem to be rather unhappy. From the experiments just cited it seems that the two disturbances do not run a parallel course throughout. Thus we found, for instance, in one of *Lombroso's* experiments relatively good absorption in spite of existing glycosuria, and in an experiment of *Fleckseder's* right good absorption in spite of a fully developed diabetes. On the other hand we find in an experiment of *Lombroso's* a not inappreciable disturbance of absorption in spite of absence of a disturbance in carbohydrate metabolism. So much is therefore certain *that, if an internal secretion of the pancreas actually essentially influences the absorption of fat, it is not identical with the pancreatic hormone regulating carbohydrate metabolism.* As we shall see later, the same is true of the observations on human diabetes.

In men the relations are on the whole much clearer than in the dog. Here we find cases with severe lethal diabetes and high-grade isolated disease of the insular apparatus; in spite of this, in these cases the characteristic, not-to-be-overlooked, fat stools are absent. On the other hand, when the pancreatic juice is completely cut off, fat stools occur, as we shall see later, which improve considerably on the administration of pancreatin. Characteristic of these pancreas stools in men is the deficiency of the splitting of neutral fat, whereas in the dog, according to the statements of all investigators the splitting of fats is not essentially disturbed even after the total extirpation of the pancreas.

In reviewing the information at hand up to the present time, we find, according to my opinion that we can thus far say with certainty, only that the absorptive activity of the intestinal mucosa *is somehow influenced by the pancreas even when the pancreas is entirely separated from the intestine,* that, however, *this influence is independent within wide limits of that of the carbohydrate metabolism through the pancreatic hormone.* At all events, I do not regard it as proper that these not at all negligible relations should be used as a basis against the teaching of the functional independence of the glandular and the insular apparatus. For this independence speak the known transplantation experiment of *Minkowski, Gley, Thiroloix, Hedon.* When we pass these in review from the standpoints above mentioned, we see that the production of pancreatic juice, therefore the function of the glandular parenchyma, is quite independent of the disturbance in carbohydrate metabolism. The glandular parenchyma of the transplanted piece may atrophy, the secretion from the fistula may stop flowing, and yet the diabetes remain absent. Only after extirpation of the sclerotic piece (with the retained islands) does the diabetes set in. On the other hand, there is known the experiments of *Thiroloix* in which diabetes set in after the transplantation, in which case therefore the islands probably suffered harm, while the secretion continued to flow from the fistula.

I do not subscribe to the critical remarks of *Lombroso* directed against the remaining refractory of the insular apparatus after duct ligation. It seems to be intelligible that the chronic inflammatory processes that occur after ligation of the duct, may under certain circumstances damage also the insular apparatus and on account of this lead transitorily to glycosuria. There is no longer doubt as to the fact, now communicated from all sides, that also a long time after the ligation of the duct the entire glandular apparatus becomes sclerotic, the insular apparatus remains entirely or largely retained, and that on this account disturbances in carbohydrate metabolism remain absent. The experiments on pigeons that *Lombroso* quotes as support of his position are not convincing. In these experiments although the insular apparatus was apparently markedly damaged, the glycosuria remained absent. As *Biedl* has already pointed out, however, in many species of birds, the total extirpation of the pancreas does not lead to glycosuria, but only to hyperglycemia. The experiments on transplantation of the pancreas and the institution of a pancreatic fistula seem to me to be especially poorly adapted for the decision of this question. If the healing follows by primary intention the carbohydrate metabolism and also the insular apparatus do not alter. If, however, infection occurs and on account of this infection sclerosis of the pancreas sets in, naturally the insular apparatus can also be damaged, and often it would be very hard to estimate in such an altered pancreas the functional integrity of the tissue constituents still present. I have carried on some experiments that in spite of the unfavorable relations seem to me to point to the functional independence of the two apparati.

*Zuntz* and *Mayer* found in their pretty experiments that the ligation of the excretory duct led in the dog first to a more or less well-expressed loss of body weight. Mostly the dogs rapidly regain their body weight and then live from then on like normal dogs. In other cases, however, the body weight falls still further, the emaciation terminating in death. Now *Zuntz* and *Mayer* found an almost complete disappearance of the glandular acini in these dogs, while in the dogs that recovered the disappearance of the glandular parenchyma proceeds much more slowly. *Zuntz* and *Mayer* conclude from this that in addition to the production of the pancreatic juice and of the still hypothetical hormone regulating carbohydrate metabolism the pancreas has still another function, by which it becomes concerned with general metabolism. Cannot fat necroses, that are known to be difficult to avoid in the operation on the pancreas, have played a part in the sudden death of the dogs?

I should like to summarize the results of the experimental investigation up to the present in the following propositions. *There is probably produced from the insular apparatus of the pancreas a hormone that is given principally to the venous blood and carried to the liver. When this hormone is absent, marked excretion of sugar and disturbance of glycogenesis occurs.* Further there occurs elimination of ketone bodies. The decomposition of albumin and the excretion of salts, and again the production of calories is highly increased, and finally there occurs an increased excitability of the sympathetic nerves.

According to my view, there speaks for a disturbance of glycogenesis, in addition to the marked poverty in glycogen, especially the fact that we have in partial extirpation of the pancreas (*Sandmeyers's* diabetes) the occurrence of a glycosuria only on alimentary overfeeding. In the several forms, at the height of the metabolic disturbance the glycogen formation in the liver seems markedly reduced. For this speaks the observation, as already *Minkowski* found, that the administration of dextrose raises the sugar-elimination to about the amount administered and also the demonstration furnished by *Grote, Staehelin* and *myself* that administration of sugar does not increase the respiratory quotient. That glycogen formation is not entirely in abeyance is spoken for, among other circumstances, by the fact that we may still obtain it on the adminstration of levulose.

In my opinion there speaks for an overproduction of sugar the fact that also in fasting, when the alimentary influences are entirely ruled out, sugar production proceeds in the liver with the intensity that it does.

Finally there remains for discussion the question as to whether the overproduction in the liver is alone the cause of the sugar elimination or whether also the combustion of sugar in pancreatic diabetes is diminished or increased. An attempt has been made to reach nearer the solution of this question by investigating whether muscular work will reduce the elimination of sugar. The basic investigation of *Seo* have shown that after incomplete extirpation of the pancreas sugar elimination as well as the quotient D:N diminishes under the influence of muscular work. After complete extirpation of the pancreas no such diminution occurs. If a shorter period be investigated, there rather occurs an increase in the quotient. If in such an animal the elimination of sugar at a later stage has started to fall, there occurs as a result of muscular work an increase in the quotient even above that regarded as the maximal boundary. From this *Seo* concludes that the increase in the consumption of sugar on account of muscular work is only possible when pancreatic tissue is still present in the organism. This conclusion is not, however, very convincing. *v. Noorden* explained analogous observation in human diabetes by the fact that as a consequence of oversensitiveness of the sugar-forming apparatus the steady appeal of which to the liver for much sugar during muscular work is answered in an excessive manner.

The fact that the respiratory quotient after total extirpation of the pancreas was maintained at a very low level, and, as previously mentioned, remains at this level in spite of administration of carbohydrates, was formerly regarded as a chief argument for the disturbance of carbohydrate combustion. *v. Noorden* mentions, however, that it has not as yet been shown that the substance that undergoes combustion in muscle is not a sugar. It has only been shown that the excretory product is not a nutritional carbohydrate; it may, however, be a fat.

Also other authors express themselves as against a disturbance in sugar combustion. *Chauveau* and *Kaufman* investigated the sugar contents in the arterial and venous blood of pancreasless dogs, and found that of the arterial blood higher. Investigations on the "sugar puncture" hyperglycemia yielded the same result. *Porges* and *Salomon* found in their experiments that on exclusion of the entire portion of the body lying below the diaphragm, that the respiratory quotient in the pancreasless dog rose as high or even higher than in normal animals under the same conditions. As the combustion under these conditions takes place chiefly in the muscles, they assume that after removal of the pancreas, the muscles are in a condition to burn up sugar.

Recently *Knouthon* and *Starling* have again entered the lists for a disturbance of the sugar combustion in the pancreasless dog. If a heart-lung preparation of a normal dog is transfused with normal blood, there occurs a strong consumption of sugar. If, however, the heart-lung preparation of a pancreasless dog is transfused with the blood of this animal, the consumption of sugar straightway becomes 0. If dealbuminized pancreas extract be added to this blood, consumption of sugar reappears. *Knouthon* and *Starling* conclude from this that tissue and blood contain a substance ordinarily coming from the pancreas that is necessary for the sugar consumption in the tissues.

The experiments of *Knouthon* and *Starling* may be interpreted in two ways: Either in normal dogs the sugar is burned, or it is polymerized and assimilated. According to the interesting experiments of *Levene* and *Meyer* the latter is not at all unlikely. For these authors showed that through the combined action of muscle-plasma and pancreas extract, the power of reduction of a sugar solution becomes reduced, but may be regained on cooking with acids.

The experiments also make necessary a revision of the important investigations of *Lépine* on glycolysis.

It is very unlikely that the combustion of sugar in the pancreasless dog ceases entirely. It must not be forgotten, that very intense grades of glycosuria occur not only in human beings, but that forms of diabetes may also be produced in dogs, that are associated with a more intense elimination of sugar than is the case in pancreas diabetes. I refer to investigations of *Lusk* on phloridzin diabetes, in which the quotient 3.6 was regularly attained. Also in our investigations on simultaneous extirpation of the pancreas and thyroid gland and especially of pancreas and parathyroid glands were the quotients high. Therefore in ordinary pancreatic diabetes it must either be that less sugar is formed, or that sugar is still consumed.

If we adopt the standpoint that the combustion of sugar in the muscles is only possible after preceding assimilation, the experiments of *Starling* would show that the glycogenesis in the muscles and probably also in other cells that otherwise contain glycogen is, without the pancreatic hormone, highly reduced. A certain grade of glycogenesis is always found remaining in the pancreatic diabetic dog, as already mentioned. If we assume that in the experiments of *Porges* and *Salomon* that only the carbohydrates just assimilated is consumed to the last traces, we may readily bring it in harmony with the assumption that the assimilation of carbohydrates in the muscles of pancreasless dogs is diminished. It seems to me therefore that the two series of experiments do not unconditionally contradict each other, if the fact is emphasized that in the pancreasless dog the formation of glycogen is disturbed not only in the muscles but also in the liver.

It is very hard to explain the enormous increase of the albumin decomposition, the salt elimination, and especially also the caloric production, in the dog with pancreatic diabetes. I shall return to this in the theoretical considerations, later on.

I might summarize what I have just detailed in the following hypothesis: *The pancreatic hormone is an exquisitely assimilatory hormone, and governs glycogenesis in the liver and muscles. In the light grades of insufficiency the disturbance in carbohydrate metabolism occurs only when there are instituted great demands on glycogenesis in the liver (alimentary overloading with carbohydrates). In the severer disturbances there occurs, in addition to the disturbance in anabolism, a marked increase in catabolic processes and thereby a faulty decomposition of higher and lower fatty acids (ketonuria).*

## B. Experimental Nervous Diabetes

The experimental nervous diabetes will be mentioned here only briefly. Many important facts have already been mentioned in the chapter on the suprarenals. We have to thank *Claude Bernard* for the fundamental experiment. A puncture at a definite place in the fourth ventricle leads in many animals to a glycosuria lasting several hours. Recently *Aschner* has shown that a similar sugar center lies also further centrally in the subthalamic region. In sugar puncture the stimulus travels over the paths of the sympathetic, and leads to an unburdening of liver glycogen and to hyperglycemia. If the conduction is interrupted in the spinal cord above the giving-off of the splanchnics, or if the liver is previously rendered sugar-free, as for instance, by strychnine, the puncture is of no avail. Until up to a few years ago this is as far as the mechanism of sugar puncture had been explained, nor did we know how the impulse was carried over from the splanchnics to the liver. The investigations of the last few years have shown that the chromaffin tissue is to be regarded as the governing device. Already *Blum* had expressed the opinion that sugar puncture acted by way of the suprarenals. In common with *Eppinger* and *Rudinger*, *I* showed that in thyroidless dogs adrenalin glycosuria as well as "sugar puncture" glycosuria were not induced. Both were therefore prevented by the same factor. *Waterman* and *Smith* found after sugar puncture a mydriatic substance in the serum. But to-day we must consider the methods used by these authors for the demonstration of adrenalin as insufficient. A further analogy between adrenalin glycosuria and sugar puncture lies in the appreciable hyperemia of the liver that occurs after each procedure, as *Priestly* and *I* have pointed out. After both procedures there occurs an increase in blood-pressure (*E. Neubauer*). For the convincing experiment we have to thank *R. H. Kahn.* He showed that after sugar puncture the staining of the suprarenals to chrome dyes as well as the pressor power of the suprarenal extract decreases. If the puncture is done after previous section of both splanchnics the glycosuria remains absent, as is known, and the staining of the suprarenals to chrome dyes is retained. It was shown therewith, in confirmation of the experiments of *Nishi*, that the left splanchnic supplies both suprarenals, while the right splanchnic gives off fibers only to the right suprarenal; for on action of the right splanchnic the puncture makes both suprarenals poorer in adrenalin while on section of the left splanchnic only the right suprarenal suffers somewhat in its adrenalin contents. Electrical stimulation of the splanchnic (section of the nerves and stimulation of the peripheral stump) elicits glycosuria. *Tschebokraroff* had previously shown that the adrenalin contents of the blood of the suprarenal veins is increased by electrical stimulation of the splanchnics.

Therefore the action of sugar puncture may be explained by *an afferent impulse conducted along the splanchnics, which leads to an unloading of the chromaffin.* How adrenalin occasions a dissemination of the sugar from the liver is not as yet clear. *E. Neubauer* thought that the hyperemia of the liver was alone the cause of the dissemination of glycogen. I think, however, that against this speaks the fact that there are agents that bring about distinct hyperemia of the liver without producing glycosuria. Such an action has pituitrinum infundibulare, for instance. The hyperemia of the liver may, however, very well favor the development of a glycosuric action, as has already been dealt with in the chapter on the suprarenals. We might suppose an activation of the diastatic ferment in the liver. *Hofmeister* reports recently that after the puncture, the glycogen for the most part is no longer found in the liver-cells, but in the efferent lymph and blood-vessels. *Zülzer* first propounded the view that adrenalin and the pancreatic hormone have an antagonistic action. The poisonous action of adrenalin would be neutralized by the pancreas hormone in the liver. *V. Noorden* expressed the view that both pancreas and chromaffin tissue influence the diastatic process in a contrary manner—the pancreas inhibits, the chromaffin tissue accelerates it. *v. Fürth* and *Schwarz* have taken justified exception to the experiment of *Züzler*. *A certain opposition in the action of the pancreatic hormone and of adrenalin is, however, unmistakable. The former works assimilatorily, governing the building up of glycogen, and the latter is dissimilatory, occasioning melting down of glycogen and decomposition in sugar.* At all events we shall see later that the alimentary factor governed by the pancreas and the nervous factor working by way of the chromaffin tissue may be highly independent of each other.

According to later investigations of *Bernstein* and *myself*, I might assume that as in the liver so also in the muscular system the same regulating powers that govern assimilation and dissimilation are opposed to each other. In a large series of experiments we saw the respiratory quotient rise in human beings after the injection of adrenalin (previously *Roth* and *Fuchs* had already reported on two experiments on patients with Addison's disease). The rise in the respiratory quotient may be so appreciable that from it we may infer a combustion of an additional 30–40 gm. of sugar in the course of from half to three-quarters of an hour. As after injection of adrenalin there occurs also an impoverishment of the muscles in glycogen; I would consider most likely that under the influence of adrenalin the glycogen is everywhere mobilized and burnt[1] in a precipitate manner, whereby a greater part of the sugar is furnished precipitately to the blood from the liver, producing hyperglycemia and glycosuria. Now it is very noteworthy that in severe cases of diabetes mellitus, that had been made sugar-free, we saw after injection of adrenalin considerable glycosuria, but no rise in the respiratory quotient. Hence there is absent in the severe diabetic the power to take into combustion precipitately mobilized sugar; of course the possibility should be considered that the sugar mobilized on account of adrenalin in the severe diabetic emanates not from glycogen, but from fat; in such a case the respiratory quotient should, however, sink.

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[1] Such an increased combustion of carbohydrate seems moreover to be able to occur isolated in the muscles. I refer to the experiments with "pituitrinum glandulare" already quoted in the chapter on the hypophysis, in which there occurred a rise in the respiratory quotient, while all other actions were quite opposed to those of adrenalin (lessening of the volume of the liver, sinking of blood-pressure, no rise in blood sugar, but more often slight reduction, and finally reduction in the total caloric exchange). Also in two experiments on severe diabetes was there a rise in the respiratory quotients, while the reduction of the total gas exchange, showed with certainty that the agent was active.

## II. CLINICAL PART

Although we are informed as yet only by hypotheses as to the intimate process by which the pancreas enters into the regulation of the carbohydrate metabolism, the fact itself is not to be doubted that the pancreas belongs to the most important regulators of the carbohydrate metabolism and plays a leading rôle in its disturbances. If now we try to enter further into the question as to what rôle the pancreas or its inner secretory function plays in human pathology, we find that it is more to our purpose to view the problem from two different sides. On the one hand it will be necessary to pass in review the clinical pictures in which gross anatomical alterations of the pancreas have been observed, and to analyze which symptoms of the total symptom-complex can be referred eventually to the disturbance of the internal-secretory activity. A thorough description of these disease pictures does not lie within the province of the task I have set for myself, and is also not necessary for the purpose I am striving for; yet it seems to me desirable to delineate the same at least in coarse outlines. For as we have already mentioned in the consideration of the experimental physiology, there have been attempts to bring many symptoms that were formerly referred to as the external secretion of the pancreas, also in connection with the internal secretion. On the other hand I shall draw the essential features of the metabolic disturbance that we designate diabetes mellitus, describe the pathologico-anatomical alterations found in the condition, and discuss what rôle the pancreas plays in it.

It will be evident that there are a number of cases the analysis of which we can approach as well the one way as the other.

### A. Gross Anatomical Disturbances

An etiological classification of the diseases of the pancreas is not possible to-day. As yet we know far too little in this respect. At any rate, the rôle played by infection is important. This may occur hematogenously, or by contiguity, in which case infectious processes of the neighboring parts affect the pancreas; and finally especially in gall-stone affections (*Hirschfeld*) in which infection reaches it from the intestines through the ducts. The route last mentioned is by far the most frequent. An important rôle is played by diseases of the vessels of the pancreas and by cirrhotic process that depend on the chronic action of poisons (alcoholism, etc.). Also trauma may come into consideration as an etiological factor, especially in existing arteriosclerosis of the pancreas. Further we recognize a series of tumors of the pancreas under which carcinoma is by far the most common; further cyst formation, the genesis of which may be of various nature, and finally a congenital failure of development especially of the insular apparatus (see genuine diabetes).

An acute attack of the function of the entire pancreas may be observed under circumstances in **apoplexy of the pancreas** or in **acute hemorrhagic pancreatitis.** The first occurs chiefly in old corpulent drunkards with advanced arteriosclerosis. In association with suddenly onsetting abdominal pains there occurs distention of the abdomen in the epigastrium, retention of feces, vomiting, and finally, with distinctly pronounced manifestations of ileus, death in the course of a few hours or days. Section shows enormous blood effusions in the pancreas, and eventually into the abdominal cavity, as the consequence of hemorrhage from the pancreatic vessels. The course of the disease is for the most part so fulminant, that glycosuria mostly does not occur even on complete destruction of the pancreas.

Acute hemorrhagic pancreatitis usually sets in with acute gastric disturbances after indefinite prodromal symptoms that have lasted for some time; to the gastric disturbances are rapidly added distention of the epigastrium, violent pressure pains in the pancreatic region and high fever; either death follows rapidly under the manifestations of acute ileus and perforation peritonitis, or the case comes to remissions; then usually the disease lasts a longer time. Symptoms, that depend on falling away of function of the pancreas are not rarely observed. In a case that proceeded rather acutely, I found 12 per cent. of sugar in the urine. In this case the reduction of the copper sulphate took place even in the cold. An interesting case with a chronic course is described by *Albu*. In a twenty-nine-year-old woman who had formerly often suffered with violent pains in the gastric region there gradually developed in association with rise in temperature a resistance in the epigastrium, fat-stools, and glycosuria. After a transitory improvement, the manifestations grew worse again, and a piece of necrotic pancreas tissue was removed on operation. A second operation was necessary on account of suppuration of the gall-bladder, after which the febrile process ceased, the fat-stools and the glycosuria disappeared, and after some time there was a recurrence of the fat-stools, and of the sugar up to 5 per cent.

Acute hemorrhagic pancreatitis was first described by *Balser*. Later the clinical picture was accurately described chiefly by *Körte*. According to the recent experimental investigations it is to be assumed that there first occurs necrosis of the pancreatic tissue through infection from the intestine or through the pancreatic duct (*Körte*, *Opie*) on account of nutritive disturbances, and then this goes on to fat necrosis through the action of the pancreatic juice. The fat necrosis probably travels further by way of the lymph channels, and then the pancreatic secretion gets into the circulation and acts toxic (*Gulecke* and *v. Bergmann*). Disturbances in sugar metabolism are to be expected, only if the process involves the greater part of the gland and is not too fulminant.

It is very probable the **chronic inflammatory processes** of the pancreas occur more frequently from infection through the pancreatic duct than we had previously supposed. *Hirschfeld* described three cases in which at the end of an influenza or of febrile angina there occurred either swelling of the liver and gastric distress or colicky pains and glycosuria of 2 to 6 per cent. After lasting one to five months the pains disappeared. Sometimes chronic pancreatitis occurs in cholelithiasis, although in this case the insular apparatus is affected only rarely. *Mayo Robson* found only four cases of diabetes (0.2 per cent. to 0.4 per cent. sugar) among sixty-five cases with stones in the ductus choledochus and with hard enlarged pancreas. In three cases the sugar vanished after the operation. Later one case passed into severe diabetes.

Before I enter more intimately into chronic pancreatitis and pancreatic cirrhosis, I would mention a special form of it, namely, the luetic. The hereditary syphilitic form is apparently chiefly interstitial, and avoids the insular apparatus, on which account it almost always pursues its course without sugar. The syphilitic pancreatitis of adults is either gummatous (*Hernheimer*, *Hirchfeld*), or interstitial. The latter form, if it progresses, may also temporarily damage the insular apparatus and thus lead to glycosuria. *Chrelitzer*, *Ehrmann*, *Albu et al*, report such cases. In the case of *Chrelitzer*, a relapse of lues occurred ten years after the primary affection. Simultaneously with the exanthema occurred abdominal pains radiating toward the back, vomiting, meteorism, jaundice, swelling of the liver and rise of temperature. A hard tumor was palpable deep between the navel and the xiphoid process. In the urine was found 2.2 per cent. of sugar. Cure occurred spontaneously. In *Ehrmann's* case an extremely severe diabetes (8 per cent. of sugar, acetone) developed at the time of the outbreak of a syphilitic exanthema. The inunction cure was interrupted and an antidiabetic regimen introduced. All symptoms disappeared within eight days. *Albu's* case was very chronic. In a forty-four-year old man (primary affection fourteen years previous) there developed gastric disturbances, emaciation, jaundice and enlargement of the liver; after a longer time, fat stools and glycosuria (0.9 per cent.); also a tumor was palpable deeply. Under enemas of potassium iodide, and pancreatin, improvement occurred; and after several months tumor and glycosuria disappeared and the case was cured. In general, lues does not play a great rôle in the etiology of diabetes. *v. Noorden* found syphilis in the history of 1.2 per cent. in male individuals under twenty years of age, 7.1 per cent. in males over twenty, and 2.3 per cent. of female diabetics of all ages.

*Chronic indurative pancreatitis* is a very common disease. It may proceed from the vessels (arteriosclerosis, endarteritis obliterans) or from the excretory ducts. It may be diffuse or circumscribed. In gall-stone affections there may sometimes occur isolated sclerosis of the head of the pancreas

(*Riedel*). Chronic indurative pancreatitis often occurs simultaneously with atrophic cirrhosis of the liver, especially in alcoholics. *Weintraud*, *Bence*, and *others* have described such cases, in which as a result of high-grade deficiency of pancreatic function there occurred pronounced disturbances of fat absorption. In *Bence's* case severe diabetes existed. The section showed a marked disappearance of the pancreas, and sclerosis; the islands of Langerhans were entirely destroyed, and only remnants of the acinous tissue were present. In very severe alcoholism there exists simultaneously sclerosis of the liver and pancreas (and suprarenals), sometimes associated with the deposition of iron-containing pigment in the liver, pancreas, skin, etc. (cirrhose bronzée or diabéte bronzée). Atrophy of the pancreas with sclerosis is a common finding in diabetes mellitus. When it occurs the insular apparatus is mostly rather severely damaged. We shall come back later to the consideration of *v. Hansemann's* granular atrophy of the pancreas and the interacinous sclerosis of *Opie*, and the sclerosis periacinous of *Lépine*, *Lemoine* and *Lannois*. In severe damaging of the glandular parenchyma, there may in such cases occur disturbances of absorption. In the case of *Keuthe*, that had previously been described by *Glässner* and *Siegel*, there existed a moderate disturbance of the fat absorption (the fat in the diet was slight only) and several times transitory glycosuria (of 0.3 per cent. to 0.7 per cent.). The autopsy showed marked atrophy of the pancreas, the duct of Wirsung was not to be found, the islands of Langerhans were in part retained or were hypertrophied. Sometimes the marked sclerosis of the pancreas is the result of a **lithiasis pancreatitis.** Lithiasis of the pancreas may occur isolated; but not rarely it is combined with cholelithiasis. In certain cases kidney stones were also found. In this event, we may speak of a general stone diathesis, that not rarely is familial. The pancreas stones are whitish, brittle, crumbly, unlike gall-stones they contain no pigment, but on the contrary are rich in lime-salts, so that under circumstances they can be demonstrated by the X-rays. Probably they usually originate (as do gall-stones) after a chronic catarrh has established in the duct system of the pancreas. Often the larger and smaller pancreatic passages are plugged up with stones. In other cases there are found one or more larger stones, which pass with severe colic, and may temporarily or permanently block up the larger ducts of the pancreas, or even the principal excretory duct. Behind the place where the stone lodges there often occurs a dilatation of the passage in question and an indurative pancreatitis, which at the beginning affects the islands but little, but on longer duration damages them severely. The pancreatic colics that *Minnich* first described intimately commence with severe girdle-like pains radiating to the back and even to the shoulder. In a case that I saw, the girdle-like pains associated with symmetrical hyperesthetic zones over the iliac crests led me to think of a spinal affection, until on the next day the occurrence of very voluminous stools with creatorrhea and steatorrhea made possible the diagnosis of occlusion of the duct of Wirsung by a pancreatic stone. The impaction of a pancreatic stone can also take place without pains. This was the case in a patient observed by *Gigon* and *me*. Also here there recurred from one day to another all the acute absorptive disturbances characteristic of impaction of a pancreatic stone, without, however, the existence of colic. At autopsy there was found in addition to numerous small stones in the pancreas a stone the size of a cherry stone which fully occluded the place of opening of the pancreatic duct into the ampulla of Vater.

The high-grade indurative pancreatitis that so frequently complicates stone of the pancreas, especially on the occlusion of the chief excretory duct by a stone, makes intelligible the fact that lithiasis of the pancreas is so frequently associated with disturbances of the sugar metabolism. *Oser* reports that among seventy cases, diabetes or at least temporary glycosuria was observed in twenty-four, that is, in more than 34 per cent. of the cases. *Lazarus* indeed found it in 45 per cent. *Albu* mentions an interesting case. The test for alimentary glycosuria had previously resulted negative. There existed a tumor in the region of the pancreas which distinctly enlarged during a severe attack of colic. On test for alimentary glycosuria, 2.9 per cent. of sugar was found in the urine. In the case of mine previously mentioned a slight diabetes existed before the colic. The patient could easily be made sugar-free by a strict diet. After the colic and the occurrence of the fat stools, the diabetic metabolic disturbances became essentially worse; after about eight days the voluminous stools disappeared; after another two weeks the stools were entirely normal, even after heavy overloading with fat; simultaneously with this there was also observed a retrogression of the diabetic metabolic disturbances, so that the patient again became temporarily sugar-free. Apparently as a sequel of severe inflammatory processes in the ducts, the islands of Langerhans do not, in occlusion of the duct of Wirsung by stone, behave so refractory as in animal experimentation after ligation of the excretory ducts. It is also of importance for the occurrence of disturbances in sugar metabolism, whether the second pancreatic duct is obliterated or is likewise closed by a stone, or whether numerous intrapancreatic passages are rendered impassable; as the intensity and the extensiveness of the sclerotic processes are in part dependent on these factors.

The circumstances are also important for the occurrence of disturbances of absorption. It is without other considerations to be expected that these only become manifest in a pronounced manner when the flow of pancreatic juice into the intestine either is fully interrupted, or at least almost completely ceases. I would like to enter here upon the question as to the relationship that exists between the disturbances of absorption that occur on cessation of the pancreatic juice in man, and the internal secretion of the pancreas. At the beginning, when the animal experiments of *Abelmann* were regarded as indicative, the question seems to have become entirely cleared We referred the occurrence of absorptive disturbances to the absence of the pancreatic juice, the occurrence of glycosuria to insufficiency of the internal secretory activity of the pancreas. In more recent times this question has encountered confusion in the literature. Naturally there occur disturbances of fat and albumin absorption when the production of pancreatic juice is normal, as in profuse diarrheas of different origin, amyloidosis of the intestine, etc. We know further the disturbances of fat absorption in complete cutting off of the bile from the intestine and also the fat stools in certain forms of Basedow's disease; as important differential criteria against both the last-mentioned forms are, since *Friedrich v. Müller's* investigations and the observations of *v. Noorden's* clinic as to Basedow's disease, the disturbance in fat decomposition that occurs on the cutting-off of the pancreatic juice and again the slight holdings in soaps. To this should be added the fact that in typical pancreatic stools, the creatorrhea, that is the more prominent occurrence of striped muscular fibers, dominates the microscopical picture. With this is associated a more distinct loss of nitrogen by way of the feces than is observed in other disturbances of absorption. Finally there have been worked out a series of methods for demonstrating the absence of a proteolytic or amylolytic ferment in the feces obtained after purgation. Many authors have raised objections to these diagnostic postulates, as they have observed cases of disease of the pancreas in which the characteristic disturbances of absorption were absent, in spite of complete cutting-off of the pancreatic juice from the intestine. Thus *Deucher*, *Albu*, *Ury*, *Alexander*, *Keuthe* and *Brugsch* saw normal fat splitting in pancreatic diseases. Also creatorrhea is sometimes absent. We might suppose that in these cases the other digestive ferments have entirely taken over the rôle of the pancreatic secretion. *Brugsch* explains that on simple occlusion of the excretory duct of the pancreas there occur no, or only temporary, absorptive disturbances, but more intense disturbances only when the pancreas is completely degenerated or the gland tissue is for greater part destroyed through carcinoma or abscesses, etc. Then only would loss of fat occur up to 60 per cent. and the nitrogen loss up to 20 per cent. This hypothesis, which has indeed not been based on the examination of a definite case, but has been influenced by the views of *Lombroso* which we have already criticised, is not decisive. I refer only to the previously mentioned case of *Gigon*, in which the absorptive disturbances set in suddenly on occlusion by stone and lasted until death. The pancreas cannot degenerate in a day; if, however, it has already been markedly degenerated, we cannot readily see how it can have furnished sufficient secretion up to the day on which the occlusion occurred. Too, it seems especially inappropriate to apply off-hand to human pathology the results of animal experiments, which as we have seen are not as yet fully explained. It would indeed be conceivable that the other digestive secretions in the dogs render the pancreatic secretion less indispensable than in man. In human pathology, the conditions seem to me to be clearer and to justify a single standpoint. *v. Noorden* and *Salomon* have pointed out in this regard that in cases of absence or insufficiency of the pancreatic juice, the absorptive disturbances become manifest, if the intestine is overloaded with fat; if in this functional test, butter stools occur we may take it for granted that there is certainly a disease of the pancreas or absence of the pancreatic juice. Also this is true if creatorrhea makes its appearance. It should not be forgotten that in many of the cases of pancreatic disease in the literature (especially in carcinoma, in which fat stools are absent, on account of the increasing cachexia), the intake of diet was very slight at the time of the observation. We must here again refer to the anatomical relations of the duct system. We must consider that if the second duct of the pancreas is not obliterated or occluded, enough pancreatic juice may still reach the intestine, even if the principal duct be completely occluded, that the disturbance does not become manifest even on heavy overloading. As far as the fat splitting is concerned, *Salomon* has pointed out that during the tedious procedure of drying the stools on the water-bath, always more fatty acids occur. If we do not take this into account, we may arrive at entirely false values for fat splitting. We may summarize by saying that markedly lessened or absent production of pancreatic juice, or cutting-off of the pancreatic juice from the intestine, leads in man to characteristic absorptive disturbances.

I have entered into detail into these conditions, because we require a clear formularization if we wish to enter into the question as to how far the internal secretory activity of the pancreas is independent of the external secretory activity, and whether these disturbances occur isolated in the gross anatomical diseases of the pancreas. In the acutely onsetting, severe damagings of the organ (suppurative or acute hemorrhagic pancreatitis, necrosis of the pancreas or apoplexy of the pancreas) it is intelligible that we do not see much of the disturbance of the external or internal secretory activity of the pancreas. Often, too, in complete extirpation of the pancreas in animal experimentation, the sugar does not occur immediately if septic processes are present at the same time. When diet is low or not ingested at all, of course the absorptive disturbances do not occur either. If the course is subacute, as a rule both disturbances are present. In tumors of the pancreas, the behavior of the disturbances varies very much. Cysts may leave behind sufficient functionating pancreatic parenchyma and hence may pursue their course without any disturbance whatsoever. If the greater part of the pancreas takes part in the process sympathetically, a latent insufficiency of both functions may develop that may eventually become evident only on overloading; although it is intelligible that in individual cases on account of especial anatomical relation the absorptive disturbances may become more distinct through compression of the duct system. In carcinoma of the pancreas it seems that the islands of Langerhans hold out longer against the carcinomatous infiltration than do the acini. As the carcinoma usually is seated in the head of the prancreas it not infrequently happens that there is complete shutting off of secretion through compression of the chief duct and hence a distinct prominence of absorptive disturbances. We should consider, of course, that the ingestion of food in such a case is very slight on account of the cachexia.

In carcinoma we not rarely observe, in addition to this that the intensity of the glycosuria diminishes with increase in the cachexia, or the sugar entirely disappears. This is entirely comprehensible. We see even in the pancreasless dog the glycosuria diminish, if with the weakening of the liver processes the mobilization of sugar is also less. In slight grades of chronic indurative or more atrophic pancreatitis no disturbances in carbohydrate metabolism need necessarily be present. In advanced cases it may very well be assumed that the function of the insular apparatus has often suffered previous damage and has thus led to disturbances in the sugar metabolism. We shall see later that this form of pancreatitis not rarely forms the pathologico-anatomical stratum for the "genuine" diabetes mellitus. In this, as is well known, no absorptive disturbances occur, although the antidiabetic diet mostly means a considerable and permanent overloading of the fat absorption. In former times this was associated with a heavy overloading of the intestine with meat. Thus can the production of pancreatic juice be strongly limited without disturbances of absorption becoming manifest. These occur only with the higher grades of atrophy of the pancreas. The most important are the cases with occlusion by stone, and those of consecutive sclerosis. In stoppage of the duct by stone we have in addition the suddenly appearing characteristic absorptive disturbances, that are fully developed, and most often the latent or manifest disturbances in carbohydrate metabolism that had already been present, perhaps because the catarrh of the duct system has for a long time led to incrustation of the ducts and to indurative pancreatitis. There are however cases in which, at least at the beginning, there exist fully developed disturbances of absorption but only minimal latent disturbances of carbohydrate metabolism. These cases are entirely intelligible, if through impaction of a gall-stone or through other factors leaving the pancreas for greater part intact, the supply of pancreatic juice is interrupted. *Ehrmann* and *others*, have described such cases. As example I submit the following:

*Observation LXVIII.*—R. M., thirty-five years. Entrance into the clinic Nov., 1911. Until one and one-half years ago the patient was entirely well. Then obstipation that often lasted four or five days set in, and also slight headache. For about seven months severe colicky pains in the right hypochondrium, about ten days after this jaundice, that has lasted until to-day. Since this time four or five bowel movements daily that were very voluminous, "more than he ingested as food." The stools are clay-colored. In spite of this fact the appetite remained very good, the patient fell off rapidly. The patient is almost entirely impotent. More severe jaundice, hair on head very much thinned out, that in the axillæ almost entirely absent, sparse on the pubis. Colossal hydrops of the gall-bladder. In addition, in the middle line, very deep, is a resistance hard to outline. Ascites.

Röntgen examination: diffuse aortic extension of a moderate degree. Wassermann negative. Increased peristalsis of the stomach, although emptying of the stomach is not essentially slowed. Urine deeply jaundiced, no sugar. Chemical examination of the stomach contents normal.

The stools (3–4 daily) are very massive and are acholic; urobilin test constantly negative; minimal, quantitatively not estimable amounts of urobilogen (*Dr. Charnas*). The stools are of gray-white color, glittering with fat, of very foul odor, microscopically show much neutral fat, soap and fatty acid needles and striated muscle fibers. By loading with fat (250 gm. oats, oatmeal, and 300 gm. butter) there occur typical butter stools. The test was repeated five times always with positive results.

The chemical examination of the stools (with the overloading test) showed 38.5 per cent. unsplit fat and 64.2 per cent. fat in the form of fat acids and soaps. The chemical examination of the butter-stools showed 71.7 per cent. neutral fat.

The examination of the stool for tryptic ferment according to *Gross*, and also for diastatic ferment according to *Wolgemut* showed only traces. In one examination, however, there was found slight, but distinct tryptic and diastatic action.

Five tests for alimentary glycosuria (100 gm. of dextrose, fasting) were always negative.

During the stay at the hospital there often occurred colicky pains in the gall-bladder region.

The ascitic fluid had a specific gravity of 1012, 8 per cent. albumin. The albumin bodies precipitated by acetic acid were present only in traces.

The *Salomon-Saxl's* carcinoma reaction was positive.

Although the *Salomon-Saxl's* test as well as the ascites spoke for a new growth, yet the possibility of an occlusion of the ductus choledochus by stone could not be excluded; so that the patient was operated on. There was found at operation, deep down in the abdominal cavity, a tumor whose situation was not quite clear. Cholecystogastrostomy was done. Death occurred some weeks afterward. Section showed a scirrhous carcinoma of the head of the pancreas, with closure of the pancreatic duct, marked dilatation of the passages in the body and tail of the pancreas. The ducts were filled with a milky yellowish fluid. The ductus choledochus was occluded about 1½ cm. above the papilla of Vater, and there was marked dilatation of the bile ducts above it.

The case described fulfills all the conditions that we could establish at a physiological experiment. *There are present all symptoms that are characteristic for the cutting-off of the pancreatic juice (and the bile), while the carbohydrate metabolism was entirely normal even on heavy overloading.* Such cases have an important significance. They show us that in human beings *the internal secretory and the external secretory activity of the pancreas are fully independent of each other within wide limits.*

## B. Genuine Diabetes Mellitus

It is not my intention here to depict the symptomatology of diabetes mellitus in exhaustive fashion. Much more will I limit myself merely to sketch the clinical picture, giving only somewhat more space to the metabolic disturbances, in order to discuss later the position of the pancreas in the pathogenesis of diabetes mellitus.

**The Carbohydrate Metabolism.**—Among the symptoms of diabetes mellitus, glycosuria is the most striking for physician and laity. Theoretically and also more practically important, certainly is hyperglycemia, for glycosuria is only a result of this. There is in diabetes mellitus an excretion of sugar without hyperglycemia but not rarely does there occur hyperglycemia without excretion of sugar. If the diabetes has existed for a long time, the kidneys lose their finer sensitiveness for the heightening of the blood-sugar contents, they gain in sugar-imperviousness (*v. Noorden, Liefmann, and Stern*). There is also in such cases no proportion between the degree of the hyperglycemia and the intensity of the glycosuria. Especially is this true for the diabetes of old age. The fact is also very important, as may be expected, that the tolerance only rises when the sugar in the blood has been for a long time normal, and that a series of symptoms, that we regard as the sequel of a long-continuing hyperglycemia (furunculosis, impotence, diabetic gangrene. rheumatoid pains, etc.) only vanish when the hyperglycemia is combated,

For the assumption of diabetic disturbance of metabolism there is necessary the demonstration that the sugar excreted in the urine is grape-sugar. Further, there must be excluded a series of conditions that according to experience are associated with a temporary excretion of sugar, or at least appreciably reduce the tolerance for carbohydrates. Of such conditions I mention, acute febrile diseases, intoxication with carbon monoxide or morphine, and asphyxic conditions, etc.

It should further be considered that after copious ingestion of sugar, sometimes slight amounts of sugar are found in the urine of even normal human beings. The glycosurias in certain ductless diseases especially in Basedow's disease and in acromegaly are considered in detail in the chapters on the subject. We shall consider later the matter of nervous glycosurias (in traumatic neurosis, hysteria, neurasthenia, and in certain nervous diseases such as tabes and [general] paralysis).

I might here mention the *laws* that the excretion of sugar follows. In the great majority of cases of diabetes we can observe a narrow relation between intake of food and excretion of sugar. If we place such a diabetic on a diet of a constant composition, the excretion of sugar sets in at a definite level and maintains it for a long time. In cases that have not advanced entirely too far, it is known that the tolerance may be influenced by a corresponding diatetic régime. If the patient on account of the limitation of the sugar-forming material becomes sugar-free and if the amount of sugar in the blood remains for a long time normal, a reparation occurs, so that later a diet without glycosuria may be borne that formerly led to sugar-excretion. On the other hand the tolerance is depressed when a high sugar-content of the blood has for a long time existed.

It is known that the individual food-stuffs are not equivalent in their action on the glycosuria. Carbohydrates and albumin act more positively on the glycosuria than fat, while alcohol for instance does not influence the glycosuria. Also the individual carbohydrate and albuminous bodies show differences in their action. Of the kinds of sugar, maltose, for example, acts more glycosuric than glucose, and this again acts more strongly than levulose. However, the individual diabetics do not behave the same throughout. For example, milk-sugar is borne very well by many, others react to it with a severe excretion of sugar.

Also the individual protein bodies influence the glycosuria in different manners. To mention only a few examples, casein and meat-albumin act more on the glycosuria than plant-albumin and egg-albumin, the latter acts less glycosuric when it is ingested in its native condition. The foundation for this lies partly in the fact that the individual albuminous bodies are drawn into decomposition at different rates. In very severe cases of diabetes the differences vanish, however. Otherwise the individual diabetics act differently with regard to the administration of albumin. Especially severe cases often react to increase of the ingestion of albumin with a sugar elimination relatively stronger than on the administration of carbohydrates—"albumin-sensitive cases."

The question whether in human diabetes sugar can be built out of albumin has been energetically discussed. On the clinical side it has been shown that severe cases of diabetes mellitus that have been kept for months on exclusively meat-fat-diets, constantly excrete so much sugar that it is hardly possible to refer this to the slight carbohydrate-content of the diet and to the original glycogen-content of the organism. It is further known that in especially severe diabetics the excretion of sugar varies simultaneously with the ingestion of albumin. The question of sugar-formation out of albumin can to-day be answered with a "yes" On the contrary the question as to what extent the normal or the diabetic organism can build sugar out of albumin cannot be safely decided with the methods of investigations of metabolism to-day at our disposal. We cannot in this manner make sure as to the origin, as far as ingested food materials is concerned, of the sugar eliminated in the urine. It is very probable that the sugar also appearing in the urine in slight cases does not only depend on the change in carbohydrates, but also on that of the albumin. Theoretical considerations that I shall not enter into here, speak for the fact that from 100 gm. of albumin (about 16 per cent. nitrogen) not more than 80 gm. of sugar can be formed. From 1 gm. of N. therefore would come about 5 gm. sugar.

The question is much more complicated by the fact that we have, too, to regard fat as a sugar-former. At all events, however, the administration of fat does not ordinarily increase the excretion of sugar. On these facts the diabetic treatment of diabetes is for most part built. This is readily understood when we consider, that, as *v. Noorden* emphasizes, the fat is transmitted to the blood and the tissues especially by the lymphatic paths and from there is transported to the liver only in accordance with needs, while carbohydrates and albumin directly flow to the liver through the portal vein and increase the condition of irritability of the liver. The facts that, apart from theoretical considerations, speak for the formation of sugar from fat: In severe cases of diabetes mellitus we sometimes observe a not inappreciable increase of sugar elimination when we administer large quantities of fat during a hunger period. In such cases the dextrose to nitrogen quotient sometimes raises to 10. Further cases are known in which on abundant ingestion of fat the dextrose to nitrogen quotient is found higher than in the period of less fat ingestion. Finally we have the results of exact metabolism investigations in cases of very severe diabetes, which show that for long protracted periods so great quantities of sugar are eliminated that these cannot be explained by the changes in albumin and carbohydrates. *v. Noorden* has therefore mentioned that the conclusions drawn from the dextrose to nitrogen quotient as to the extent of the formation of sugar out of albumin in human diabetes, are faulty, as we do not know the source of the sugar.

In one group of diabetics this regularity, as just described, between the sugar-value of the food and sugar eliminations exists in much less well expressed manner; indeed it may even happen that this law may be broken down by other factors. I shall describe in detail later the nervous glycosurias dependent on organic foundations. I shall cite here only the psychical factor. Any psychical agitation, a fright, a great excitation on account of a case of death in the family, or business cares, can suddenly lead to an outbreak of the diabetes. The glycosuria may attain a high grade; lassitude, great thirst, polyuria, induce the patient to consult the physician, who then finds sugar.

Often a slight limitation of the diet suffices to bring about a disappearance of the sugar, or the sugar disappears spontaneously. In a short time, normal tolerance is reestablished. At all events such cases as just mentioned are exceptional. Ordinarily, also in this group of cases is the alimentary factor plainly to be recognized; but this is small in comparison with the psychical factors. In such cases we see not rarely that painful affections of any sort at all may serve to increase the excretion of sugar. I naturally will not say concerning the category of cases in which the alimentary factor dominated the scene, that also psychical excitements may not temporarily lower the tolerance. In the nervous cases, however, the nervous factor predominates.

**The Albumin Metabolism.**—The question of albumin need in diabetes has been studied in numerous metabolism investigations. In light and moderately severe diabetics the albumin need is certainly not increased; and even in severe diabetics, as long as they are nourished rationally, we cannot speak of an increased need for albumin. This has long been shown by the protracted investigations of *Weintraud*. In a series of severe cases, I have investigated the nitrogen elimination on the "hunger" day and found values that do not differ from those furnished by normal individuals under like conditions. The severe diabetic, he who rationally fed, remains constantly on a diet rather poor in albumin, can indeed enter upon a strikingly low albumin need, and shows, when abundant albumin is now administered, a striking tendency to retention of nitrogen. Only in the severest cases, before the fatal coma, does the melting down of albumin seem to raise to a high degree.

*Benedict* and *Joslin* calculate the nitrogen elimination per kilogram of body weight in their fasting-experiments, and find that the average of all in these experiments is higher than in normal individuals; yet much might be said in objection to the calculation per kilogram of body weight, as the relation between protoplasm and body-mass becomes disarranged in severe diabetics on account of the extreme poverty in fat.

In the severest cases also the high elimination of endogenous uric acid indicates a marked melting-down of muscle albumin (*v. Noorden*).

The qualitative alterations of the albumin metabolism are, apart from the high ammonia values dependent on the becoming acid, not appreciable.

We shall here say only a few words about the **ketonuria** of diabetics. The ketone bodies originate from the change in albumin and fat substance on diminished carbohydrate combustion. The cause of this origination should not be otherwise than in a normal man when he has been fasting or has eaten meat and fat exclusively. Also in this case they are due to the lack of assimilation of carbohydrates. That in the diabetic such considerably high degrees are attained is comprehensible because in him is absent also the sugar originating from the albumin, and because they develop so very gradually. If the ketonuria lasts longer and attains higher grades, it gives rise to lipoidemia and to fattening of the liver. In the most severe grades of lipoidemia the blood may assume a light rose-red color and on standing may express a cream-like dense layer to the surface.

The alterations in the **salt metabolism** to be observed in diabetics are associated in part with the formation or the elimination of ketone bodies. Through the formation of large amounts of the ketone acids, alkalies are withdrawn from the body, and as is known, later the alkalescence of the blood sinks and then the calcium equilibrium is minus (*Gerhardt* and *W. Schlesinger*).

**The equilibrium of water** in diabetics often shows significant variations on alterations of the diet. If diabetics who formerly had fed without purpose are placed on a diet poor in carbohydrates and albumin, they often gain in weight in a short time. It is very probable that this depends not so much on the filling up of the fat deposits and partly also of the glycogen deposits, but much more on the retention of water. In more fully advanced cases the water-contents of the tissues is much reduced. *Rumpf* found the water-contents of the tissues of diabetics who had died in coma 8½–12 per cent. lower than in normal individuals.

**The Respiratory Metabolism.**—The first experiments as to the caloric exchange in diabetics are those of *Pettenkofer* and *Voit*. At the beginning, these investigators misinterpreted their experiments. They overlooked on the one hand the loss in oxygen that the diabetic suffers through the elimination of sugar rich in oxygen, and on the other hand they committed the error of comparing the change in an emaciated diabetic weighing 54 kilograms with a healthy individual weighing 71 kilograms. These objections have been set forth especially by *Leo*; *Pettenkofer* and *Voit* later modified their opinion; *Fr. Voit* again discussed the experiments in detail and came to the conclusion that in severe diabetics the demand for calories is not increased. This result is entirely in agreement of the long-protracted metabolism experiments of *Wientraud* carried out at *Naunyn's* clinic. *H. Leo*, *R. Stüve*, *Nehring* and *Schmoll*, and *Magnus-Levy* and *Salomon* have further instituted experiments with the *Zuntz-Geppert* apparatus. They found that in severe diabetics the oxygen requirements were increased. I shall not enter into the question of the experiments of *Livierato* and of *Robin* and *Binet* as the methods used are not reliable.

The interest in this question was reawakened through the demonstration that there was an increase in the production of calories in the dog without a pancreas. Since this is true a series of experiments have been published. Of especial interest is a great number of experiments that were carried out in *Atwater-Benedict's* respiration calorimeter. Finally I mention a series of experiments carried out by *Eugene DuBois* and *Borden S. Veeder* with *Pettenkofer's* apparatus at *Kraus's* clinic, and finally experiments with the *Zuntz Geppert* apparatus by *Leimdorfer*. I shall discuss later the experiments last mentioned. The experiments of *Eugene DuBois* and *Borden S. Veeder* showed no increase in heat production. These authors arrived at the same results as did *Pettenkofer* and *Voit*.

A more exact exposition is demanded by the first-mentioned experiments carried out in the respiration calorimeter. They were begun by *Benedict*, *Dr. Joslin* and *myself* in collaboration, when I had gone to Boston for the study of the respiration calorimeter. Our work in common concerned itself with the first twelve experiments. I reported briefly concerning these experiments at the Congress for Internal Medicine, 1909; and there, on the ground of the comparison of the figures obtained with those obtained with a normal subject, whom I had especially selected for comparison on account of his low body weight, came to the conclusion that the resting-exchange of the three diabetics investigated by us and especially that of one very severe case was not essentially raised. Later *Benedict* and *Joslin* on the ground of their more numerous experiments came to another assumption. Since that time I have let the matter rest on account of other work.

Only now at the preparation of this chapter have I reviewed the experiments and also the large experimental material of *Benedict* and *Joslin*, and have attained the conviction that I must hold fast to my original opinion. As the question is of importance, I shall contribute the first twelve experiments, that *Prof. Benedict* has in praiseworthy manner allowed me to publish separately in extenso. There will be found in them some details that seem to me to warrant an exact exposition.

First a few remarks concerning *method*. The experiments herewith published were carried out in a so-called calorimeter. Therefore in the fasting experiments we were concerned with estimation of the exchange in a quiet, comfortable, sitting-position. It is to be expected that the values obtained in the fasting-experiments do not fully represent the fundamental exchange, but lie somewhat higher. The figures republished by me differ somewhat here and there from those in the corresponding experiments of *Benedict* and *Joslin*. I cannot state the reason for this, the differences are however so slight that they do not influence the total result in any way. As concerns the exact details of the arrangement of the experiments, I refer to the work of *Benedict* and *Joslin*. In the tables will be found the heat-production as well as the heat-elimination. The values for the heat-elimination were estimated, by adding to the value shown by the calorimeter also the vaporization heat of the water produced (amount of produced water 0.568). The calculation of the heat production was based on the behavior of the body-temperature.

If, for example, the body temperature during an experiment rose, there was added to the amount representing the elimination of heat an amount that would be necessary to warm the person under experimentation the corresponding tenths of a degree. If the temperature fell, the loss of heat had to be subtracted from the figures representing heat elimination. Ideal values for the heat production we do not find, however, as the individual organs may possess different temperatures, and, for example, after ingestion of food the fall of heat from the liver to the mouth or rectum, where the temperatures are taken, ought to be greater than during fasting. Perhaps this is the reason that *Benedict* and *Joslin* do not give values for heat-production in their experiments.

### EXPERIMENT No. I.—PERSON UNDER EXPERIMENTATION A

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 4, 1908 | Preceding period | | | | | | | | | | | | | |
| | 7– 8 o'clock..... | 84.5 | 2.19 | 2.43 | 0.51 | 4.77 | ..... | .... | ..... | .... | .... | .... | ...... | .... |
| Fasting ... | 8–10 o'clock[1].... | 186.1 | 4.8 | 5.32 | 1.08 | 4.92 | ..... | .... | ..... | .... | .... | .... | ...... | .... |
| | 10–12 o'clock..... | 169.7 | 1.2 | 4.90 | 1.04 | 4.71 | 38.7 | 40.2 | 0.701 | 58.0 | 80 | .... | 135.8. | .... |
| | 12– 2 o'clock..... | 118.3 | 3.2 | 3.36 | 0.81 | 4.15 | 38.5 | 40.1 | 0.699 | 41.4 | 81 | .... | 137.6. | .... |
| Sum from 10 to 2 o'clock........ | | 288.0 | ..... | 8.26 | 1.85 | .... | 77.2 | 80.3 | ..... | .... | .... | .... | 273.4[2] | |

[1] The first period of 8 to 10 o'clock I have omitted, as the values in comparison with those in the later fasting-experiments were non-serial. Probably the patient, who was in the apparatus for the first time was restless.

[2] Calculated for six hours 409.1.

### EXPERIMENT NO. II.—PERSON UNDER EXPERIMENTATION A

| Date | Period | Amount of urine | Dextrose |  | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | Polarization | Titration |  |  |  |  |  |  |  |  |  |  |
| Nov. 5, 1908 | Preceding period |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 220 gm. | 7.24– 9.22 o'clock | 303.1 | 7.9 | 8.91 | 1.46 | 6.1 | ..... | .... | ..... | .... | .... | .... | ..... | .... |
| meat | 8.22–10.28 o'clock | 210.1 | 6.7 | 7.0 | 1.1 | 6.33 | 42.9 | .... | ..... | 28.6 | 84 | .... | 145.7 | .... |
| N = | 10.28–12.28 o'clock | 328.6 | 10.6 | 9.78 | 1.49 | 5.04 | 43.9 | 44.3 | 0.721 | 42.4 | 82 | .... | 148.8 | .... |
| 10.22 gm. | 12.28– 2.28 o'clock | 184.2 | 5.2 | 5.65 | 1.39 | 4.04 | 41.0 | 43.9 | 0.680 | 35.1 | 81 | .... | 140.9 | .... |
| Sum (urine from about 5 hours)... |  | ..... | 22.5 | 22.43 | 3.98 | .... | 127.8 | .... | ..... | .... | .... | .... | 435.4 | .... |

### EXPERIMENT NO. III.—PERSON UNDER EXPERIMENTATION A

| Date | Period | Amount of urine | Dextrose |  | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | Polarization | Titration |  |  |  |  |  |  |  |  |  |  |
| Nov. 18, 1908 | Preceding period<br>7 – 8.52 o'clock | 102.2 | 3.88 | 3.87 | 0.80 | 4.84 | ..... | .... | ..... | .... | .... | .... | ..... | .... |
| Fasting.... | 8.52–10.52 o'clock | 97.9 | 2.94 | 3.45 | 0.80 | 4.31 | 38.5 | .... | ..... | 47.9 | 69 | 98.1<br>98.1 | 138.6 | 139 |
|  | 10.52–12.52 o'clock | 58.7 | 1.29 | 1.36 | 0.55 | 3.00 | 37.8 | 38.2 | 0.721 | 36.3 | 67 | ....<br>98.0 | 135.9 | 134 |
|  | 12.52– 2.52 o'clock | 50.2 | 0.60 | 0.96 | 0.55 | 1.74 | 37.9 | 40.7 | 0.677 | 45.8 | 65 | ....<br>97.8 | 131.5 | 127 |
| Sum........................... |  | 206.8 | 4.83 | 5.77 | 1.90 | .... | 114.2 | .... | ..... | .... | .... | .... | 406.0 | 400 |

### EXPERIMENT NO. IV.—PERSON UNDER EXPERIMENTATION A

| Date | Period | Amount of urine | Dextrose |  | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  | Polarization | Titration |  |  |  |  |  |  |  |  |  |  |
| Nov. 19, '08 | Preceding period<br>7 – 8.50 o'clock | 117.0 | 3.74 | 3.90 | 0.85 | 4.59 | ..... | ..... | ...... | ..... | .. | ..... | ..... | .... |
| 237 gm.<br>meat = | 8.50–10.50 o'clock | 297.3 | 10.01 | 10.23 | 1.87 | 5.47 | 44.8 | 43.3 | 0.753 | 50.8 | 72 | 98.3<br>.....<br>98.5 | 155.8 | 169 |
| 9.91 gm.<br>N | 10.50–12.50 o'clock | 193.5 | 6.19 | 6.70 | 1.58 | 4.24 | 45.4 | 46.5 | 0.709 | 53.3 | 68 | .....<br>98.6 | 156.9 | 151 |
|  | 12.50– 2.50 o'clock | 134.4 | 3.76 | 4.25 | 1.38 | 3.08 | 42.2 | 44.0 | 0.698 | 45.7 | 66 | .....<br>98.1 | 151.3 | 140 |
| Sum......................... |  | 625.2 | 19.96 | 21.18 | 4.83 | .... | 132.4 | 133.8 | 0.719[1] | ..... | .. | ..... | 464.0 | 460 |

[1] Average.

### Experiment No. V.—Person under Experimentation A

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 23, '08 | Preceding period 7 – 9.20 o'clock | 68.4 | 3.42 | 4.03 | 0.59 | 6.7 | ..... | ..... | ...... | ..... | 72 | .....<br>97.8 | ..... | .... |
| 75 gm. roll + 25 gm. dextrose | 9.20–11.20 o'clock | 231.8 | 17.62 | 18.45 | 1.13 | .... | 42.4 | 41.4 | 0.745 | 58.8 | 72 | 98.0<br>98.0 | 153.7 | 154 |
| | 11.20– 1.20 o'clock | 189.5 | 14.59 | 15.44 | 0.99 | .... | 38.3 | 38.7 | 0.720 | 52.9 | 68 | .....<br>97.8 | 141.8 | 137 |
| | 1.20– 3.20 o'clock | 99.5 | 7.17 | 7.90 | 0.64 | .... | 37.3 | 37.1 | 0.730 | 48.5 | 64 | .....<br>97.6 | 132.1 | 128 |
| Sum | | 520.8 | 39.38 | 41.79 | 2.76 | .... | 118.0 | 117.2 | 0.732[1] | ..... | .. | ..... | 427.6 | 419 |

### Experiment No. VI.—Person under Experimentation A

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 24, '08 | Preceding period 7 – 9.20 o'clock | 175.6 | 5.27 | 7.46 | 1.23 | 6.06 | ..... | ..... | ...... | ..... | 70 | ..... | ..... | ... |
| 75 gm. roll + 25 gm. dextrose | 9.20–11.20 o'clock | 237.6 | 16.63 | 17.73 | 1.11 | .... | 39.8 | 42.2 | 0.687 | 58.8 | 72 | 97.9<br>98.0<br>98.05 | 146.1 | 147 |
| | 11.20– 1.20 o'clock | 214.2 | 15.85 | 16.32 | 1.04 | .... | 37.8 | 37.3 | 0.735 | 53.9 | 67 | .....<br>97.95 | 135.7 | 133 |
| | 1.20– 3.20 o'clock | 108.5 | 7.27 | 7.92 | 0.67 | .... | 37.5 | 37.5 | 0.726 | 49.1 | 63 | .....<br>97.8 | 135.5 | 132 |
| Sum | | 560.3 | 39.75 | 41.97 | 2.82 | .... | 115.1 | 117.1 | 0.715[1] | 161.8 | .. | ..... | 417.3 | 412 |

### Experiment No. VII.—Person under Experimentation B

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 9, '08 | Preceding period 7 – 9.02 o'clock | 241.3 | 10.13 | 11.49 | 1.87 | 6.13 | ..... | ..... | ...... | ..... | .. | ..... | ..... | .... |
| Fasting. . | 9.02–11.02 o'clock | 136.6 | 5.46 | 6.02 | 1.24 | 4.83 | 51.0 | 50.9 | 0.729 | 46.5 | 77 | 99.2<br>..... | 176.3 | 167 |
| | 11.02– 1.02 o'clock | 91.5 | 2.74 | 3.81 | 1.00 | 3.82 | 47.5 | 49.4 | 0.699 | 59.1 | 77 | 98.7<br>..... | 171.7 | 167 |
| | 1.02– 3.02 o'clock | 62.9 | 1.31 | 2.14 | 0.90 | 2.43 | 45.9 | 46.6 | 0.717 | 53.7 | 77 | 98.45<br>.....<br>98.95 | 160.1 | 170 |
| Sum | | 291.0 | 9.51 | 11.97 | 3.14 | .... | 144.4 | 146.9 | 0.715[1] | ..... | .. | ..... | 508.1 | 504 |

[1] Average.

### Experiment No. VIII.—Person under Experimentation B

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 10, '08 | Preceding period<br>8 – 8.54 o'clock | 214.7 | .... | 8.46 | 1.03 | 8.2 | ..... | ..... | ...... | ..... | .. | ..... | ..... | .... |
| | | | | | | | | | | | | 98.85 | | |
| Meat 13.9 gm. | 8.54–10.54 o'clock | 218.9 | .... | 7.42 | 1.07 | 7.0 | 53.7 | 57.3 | 0.682 | 41.9 | 77 | ..... | 194.3 | 196 |
| | | | | | | | | | | | | 98.9 | | |
| | 10.54–12.54 o'clock | 268.8 | .... | 9.95 | 2.12 | 4.7 | 54.2 | 57.7 | 0.683 | 67.2 | 77 | ..... | 190.1 | 193 |
| | | | | | | | | | | | | 99.0 | | |
| | 12.54– 2.54 o'clock | 168.2 | .... | 7.01 | 2.14 | 3.23 | 58.3 | 59.3 | 0.715 | 45.9 | 77 | ..... | 193.6 | 169 |
| | | | | | | | | | | | | 98.2 | | |
| Sum...... | .................. | 655.9 | .... | 24.38 | 5.33 | .... | 166.2 | 174.3 | 0.693[1] | 155.0 | .. | ..... | 578.0 | 558. |

### Experiment No. IX.—Person under Experimentation B

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 16, '08 | Preceding period<br>7 – 9.21 o'clock | 266.2 | 15.17 | 14.15 | 2.26 | 6.26 | .... | ..... | ...... | ..... | 82 | ..... | ..... | .... |
| Fasting.. | 9.21–11.21 o'clock | 152.6 | 7.02 | 7.32 | 1.49 | 4.88 | .... | ..... | ...... | 46.4 | 80 | 99.0 | 162.0 | .... |
| | | | | | | | | | | | | 98.5 | | |
| | 11.21– 1.21 o'clock | 105.4 | 4.22 | 4.75 | 1.25 | 3.80 | .... | ..... | ...... | 44.2 | 79 | ..... | 159.9 | .... |
| | | | | | | | | | | | | 98.3 | | |
| | 1.21– 3.21 o'clock | 161.2 | 2.10 | 2.53 | 0.85 | 2.98 | .... | ..... | ...... | 46.4 | 80 | ..... | 156.7 | .... |
| | | | | | | | | | | | | 98.6 | | |
| Sum.. | .................. | 419.2 | 13.34 | 14.60 | 3.59 | .... | .. | ..... | ...... | 137.0 | .. | ..... | 478.6 | .... |

### Experiment No. X.—Person under Experimentation B

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F.) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 17, '08 | Preceding period<br>I<br>7 – 8.07 o'clock | 127.0 | 7.11 | 7.19 | 0.92 | 7.82 | ..... | ..... | ...... | ..... | .. | ..... | ..... | ... |
| | II<br>8.07– 9.26 o'clock | 165.4 | 8.93 | 9.57 | 1.26 | 7.60 | ..... | ..... | ...... | ..... | 90 | ..... | ..... | ... |
| I. Chief period meat, 16.9 gm. N | 7.26–11.26 o'clock | 275.3 | 19.15 | 14.37 | 2.26 | 6.36 | 52.0 | 54.1 | 0.699 | 60.0 | 83 | 99.0 | 174.3 | 160 |
| | | | | | | | | | | | | 98.5 | | |
| | 11.26– 1.26 o'clock | 215.7 | 10.04 | 11.04 | 2.20 | 5.0 | 52.0 | 53.7 | 0.705 | 58.4 | 76 | ..... | 173.7 | 168 |
| | | | | | | | | | | | | 98.3 | | |
| | 1.26– 3.26 o'clock | 165.0 | 8.13 | 8.48 | 3.10 | 2.74 | 55.2 | 57.6 | 0.697 | 60.2 | 80 | ..... | 173.8 | 177 |
| | | | | | | | | | | | | 98.4 | | |
| Sum ...... | .................. | 656.0 | 37.32 | 33.89 | 7.56 | .... | 159.2 | 165.4 | 0.700[1] | 178.6 | .. | ..... | 521.8 | 505 |

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[1] Average.

EXPERIMENT NO. XI.—PERSON UNDER EXPERIMENTATION C

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 11–12, 1908. | Preceding period<br>7 – 8.50 o'clock | 86.8 | 2.34 | 2.66 | 1.19 | 2.23 | ..... | ..... | ...... | .... | .. | ..... | ..... | .... |
| Fasting.. | 8.50–10.50 o'clock | 95.4 | 1.72 | 1.94 | 1.38 | 1.4 | 48.9 | 46.8 | 0.759 | 46.8 | 82 | 98.6<br>98.2 | 181.7 | 172 |
| | 10.50–12.50 o'clock | 69.7 | 0.56 | 0.84 | 1.09 | 0.76 | 47.5 | 45.8 | 0.753 | 45.8 | 81 | .....<br>98.2 | 161.7 | 162 |
| | 12.50– 2.50 o'clock | 55.2 | 0.11 | 0.28 | 0.93 | 0.29 | 47.4 | 52.1 | 0.661 | 52.1 | 80 | .....<br>98.5 | 157.1 | 165 |
| Sum....... | .................. | 220.3 | 2.39 | 3.06 | 3.40 | 0.9[1] | 143.8 | 144.7 | 0.722[1] | .... | .. | ..... | 500.5 | 499 |

EXPERIMENT NO. XII.—PERSONS UNDER EXPERIMENTATION C

| Date | Period | Amount of urine | Dextrose | | N | D:N | $CO_2$ | $O_2$ | R.Q. | $H_2O$ | Pulse | Temperature (F) | Heat elimination | Heat production |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Polarization | Titration | | | | | | | | | | |
| Nov. 12–13, 1908. | Preceding period<br>7 – 8.58 o'clock | 142.4 | 5.13 | 5.40 | 1.95 | 2.7 | ..... | ..... | ...... | .... | .. | ..... | ..... | .... |
| Meat 17.39 gm. N. | 8.58–10.58 o'clock | 272.5 | 10.90 | 9.81 | 3.11 | 3.16 | 59.7 | 59.2 | 0.734 | 42.3 | 88 | 99.2<br>98.6 | 199.9 | 184 |
| | 10.58–12.58 o'clock | 244.0 | 9.76 | 10.22 | 3.58 | 2.56 | 59.8 | 58.4 | 0.744 | 66.6 | 89 | .....<br>99.0 | 196.5 | 207 |
| | 12.58– 2.58 o'clock | 157.2 | 5.66 | 5.81 | 3.07 | 1.9 | 57.4 | 57.8 | 0.722 | 46.1 | 87 | .....<br>98.4 | 191.8 | 176 |
| Sum....... | .................. | ..... | ..... | 25.84 | 9.76 | .... | 176.9 | 175.4 | 0.733[1] | .... | .. | ..... | 588.2 | 567 |

## The Fasting Experiments

The rest-fasting experiments are summarized in an easily reviewed manner in the following table:

REST-FASTING EXPERIMENTS

| Person under experiment | Date | Age | Weight | Height | D:N | $CO_2$ | | $O_2$ | R.Q. | Calories | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Per hr. | Per kg. and min. | Per kg. and min. | | Per hr. | Per kg. and hour |
| No. I. A............<br>Diabetes mellitus.... | Nov. 4... | 47 | 49.1 | 171 | (4.77)–4.92<br>–4.71–4.15 | ..... | 3.34 | 4.76 | 0.688 | ..... | 1.39 |
| No. III. A. ......... | Nov. 18 | 47 | 52.8 | 171 | (4.84)–4.31<br>–3.0 –1.74 | 19.37 | 3.06 | 4.34 | ..... | 66.6 | 1.26 |
| No. VII. B..........<br>Diabetes mellitus.... | Nov. 9... | .... | 60.0 | 173 | (6.13)–4.83<br>–3.82–2.43 | 24.07 | 3.36 | 4.76 | ..... | 84.0 | 1.40 |
| No. IX. B..........<br>Diabetes mellitus.... | Nov. 16 | .... | 60.0 | 173 | (6.24)–4.88<br>–3.80–2.98 | 22.52 | 3.14 | 4.33 | ..... | 77.8 | 1.30 |
| No. XI. C..........<br>Diabetes mellitus.... | Nov. 11 | 23 | 59.2 | 176 | (2.23)–1.40<br>–0.76–0.29 | 23.93 | 3.40 | 4.76 | 0.722 | 83.17 | 1.45 |
| Average............ | ......... | .... | .... | ... | ............... | ..... | 3.26 | 4.59 | ..... | ..... | 1.34 |
| A. W. W. normal..... | Mar. 21.. | .... | 57.0 | ... | ............... | ..... | 3.65 | 4.38 | 0.832 | 76.55 | 1.35 |
| A. W. W. normal..... | Mar. 15.. | .... | 57.0 | ... | ............... | ..... | 3.65 | 4.10 | 0.840 | 76.55 | 1.37 |

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[1] Average.

I laid these tables before the congress in my communication. It will readily be understood why I on the data of these experiments believed that there was an essential increase in the production of calories in diabetes mellitus.

The production of calories per kg. per hr. is on the average in the diabetics, 1.34, in the normal person, 1.345; the oxygen consumed is in the diabetic greater throughout. It is on the average, 4.59, in the normal person, 4.24.

I shall speak later as to the cause of the greater oxygen consumption in diabetics.

The carbonic acid production is on the average in diabetics 3.26, in the normal person 3.65.

Hence the production of carbonic acid is somewhat less in the diabetics.

The respiratory quotient is very low throughout in the diabetics, corresponding to the circumstance that all the cases investigated were moderately severe cases. Also the person C may be counted with the moderately severe cases.

The question that I asked myself at the reworking-up of the experiments was the following. Do there exist severe cases of diabetes mellitus that in spite of the copious elimination of sugar show no increase in heat production during fasting? As there were only a relatively few experiments at my disposal for the solution of this, conclusions as to the question were merely tentative. The diet which the persons tested received on the days before the experiments was mixed. It contained, however, neither abundant carbohydrate or albumin. As all experiments began fourteen hours after the latest ingestion of food and lasted six hours, so that the experiment lasted for the fourteenth to twentieth hours after the latest ingestion of food, the quotient D:N observed must be regarded as high. Only in person C did the quotient D:N fall almost to 0 during the period of experimentaton. In the first persons under experimentation the ammonia value was also raised very high. In person A the $\beta$-oxybutyric acid in the urine was also estimated and found in not inappreciable quantity. I have not included these figures in the tables and refer to the detailed works of *Benedict* and *Joslin.* In such severe cases, as persons A and B are, one must expect under conditions of experimentation that there would have been an appreciable result, if the heat production in severe diabetes is really increased. It was not the case, however. We have already seen previously that the chemical observations allow this result to be anticipated.

On the study of the extensive and carefully detailed experimental material contributed later by *Benedict* and *Joslin* I have arrived at the conviction that an increase of heat production in diabetes mellitus cannot be inferred also from this material. The explanation of the deviating conclusions of *Benedict* and *Joslin* is to be sought, I think, in the fact tha tthey did not take into account the difference in body weights of the normal persons and diabetics they investigated. I here quote in descending series the body weights of the normal individuals and the diabetics.

Normal individuals: 83.5–79.7–74.4–67.6–66.5–66.0–59.6–48.5.

Severe diabetics (weight during the experiment): 67.1–59.0–54.9–52.7–51.8–48.8–48.0–45.1–40.5.

A glance at this summary shows the great difference in body-weight between the normal and the diabetic individuals.

When we compare with one another the heat production of those cases that have the same body weight, we obtain the same result that I found in the preceding experiments. This is seen in the following summary:

| | Mrs. B. | Diabetic G |
|---|---|---|
| Weight | 67.0 | 67.0 |
| Height | 161.0 | 178.0 |
| Calories per kg. per hr. | 1.09 | 1.15 (bed calorimeter) |
| | L.E.E. | Diabetic F |
| Weight | 59.6 | 59.0 |
| Height | 179.0 | 176.0 |
| Calories per kg. per hr. | 1.47 | 1.39 |
| | Dr. R. | Diabetic A |
| Weight | 48.5 | 48.8 |
| Height | 167.0 | 171.0 |
| Calories per kg. per hr. | 1.39 | 1.34 |

The heights of the persons under experimentation are not entirely alike. In the cases of Mrs. B. and diabetic G the difference is indeed appreciable. In the other two pairs the difference would not signify much. In addition, in one case the difference favors the normal individual, in the other it favors the diabetic. We see from this summary *that the heat production in cases of severe diabetics does not differ essentially from that of the equally heavy normal individual.*

*Benedict* and *Joslin* themselves made the objection that their material is not uniform in respect to body weights. They sought to rule out this objection in the following experiment (Case C. S., 227). The first investigations were undertaken at a time that the patient weighed 62.4 to 65.4 kg. They found at that time a heat production between 1.23 and 1.40 per kilogram per hour. As the patient had later fallen away to 54.9 kg., the heat production (in one experiment) was 1.26 per kilogram per hour. I can ascribe to this one experiment no demonstrative value. It is a known law that in normal individuals the exchange lies higher the smaller and lighter the individual is. This is readily seen from the figures that *Benedict* and *Joslin* themselves have summarized.

Investigations with the *Zuntz-Geppart* apparatus (p. 168):

| | |
|---|---|
| Individuals between 65 and 43.2 kg. $O_2$ requirements per kg. per minute | 4.08 cc. |
| Individuals between 66 and 88.3 kg. | 3.5 cc. |

Investigations with the respiration calorimeter during sleep (p. 168):

| | |
|---|---|
| Individuals between 64.1 and 55 kg. | 4.04 cc. |
| Individuals between 66.1 and 84.7 kg. | 3.56 cc. |

There does occur in severe diabetes a circumstance moreover that must be considered especially. It is known that in the obese the fundamental exchange is relatively low, as the obese person possesses little respiring protoplasm in relation with body weight. The severe diabetic is, however, always strongly drained of water (as is shown in investigation on the water-contents of the organs of those dying in coma). Moreover in severe diabetics almost every trace of fat has disappeared from the ordinary sites of fat-deposition, as can be seen at almost every autopsy. If now in addition the albuminous constituent suffers severe damage in the later stages, the mass of respiring protoplasm in severe diabetes will be still greater in proportion to body weight. I believe, therefore, that even if on calculation per kilogram of body weight there is found in severe diabetics a slight increase of heat production, this would not mean much.

Already *Lusk* has pointed out the dissimilarity of the material compared by *Benedict* and *Joslin* and from this has drawn the conclusion that the increase of heat production found by *Benedict* and *Joslin* is less high than these authors suppose. From the calculations and discussions cited I must however conclude that the demonstration of an increase of heat production in severe diabetes, has with the material at hand, not been supplied.[1]

Now as concerns the oxygen requirements, this in severe cases of diabetes is undoubtedly increased. This may be seen in my tables. I find that the oxygen requirements with otherwise similar heat production average in the diabetics 4.59, in the normal individuals 4.24.

1. This is also to be seen in the figures of *Benedict* and *Joslin*:[2] That there is an increased heat production, however, cannot be inferred from the increased demand for oxygen. Already *Leimdörfer* mentioned that in the severe diabetic through the loss of bodies very rich in oxygen, in the urine (sugar, ketone

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[1] *Remark on Correction.*—Also in a second publication that *Benedict* and *Joslin* made a short time ago concerning this subject (A Study of Metabolism in Severe Diabetics, Carnegie Institution of Washington, Publication No. 476, 1912), this is shown in an undubitable manner. Here are found statements only as to the carbonic acid production and the oxygen requirements; in the severe diabetics there was a $CO_2$ elimination (per kg. per min.) of 3.31 cc. (according to my calculation 3.25); in the normal individual of like weight this was 3.13.

[2] In the second publication 4.54, $O_2$ per kilogram per minute in the severe diabetics as against 3.75 in normal individuals of the same weight.

bodies), the relation between oxygen consumption and carbonic acid production is disarranged. Direct calorimetry actually shows in the experiments made at the Boston Institute, that in diabetics with normal heat production, the oxygen consumption is increased.

2. In the *experiments with the administration of meat* the specific dynamic energy of the albumin and the time consumed in the decomposition of this in severe diabetes was investigated. The question can, however, scarcely be discussed, because the number of experiments is too small.

3. The experiments with the *administration of carbohydrates* seem on the contrary to be worthy of mention. In these investigations there was sought to be determined whether in short periods (two hours) the respiratory quotient did not temporarily rise. The two experiments on this subject agree very prettily. In normal individuals, on the administration of just as much carbohydrates, we would expect an increase of the respiratory quotient to nearly 1.0. In the two experiments on the diabetic the respiratory quotient was hardly influenced, however. *In the severe diabetic, therefore, the administration of carbohydrates does not suffice to increase the combustion of sugar.* These experiments agree very prettily with the experiment of *Falta*, *Grote*, and *Staehelin* on the dog without a pancreas. Also here the respiratory quotient was not increased on the administration of sugar. In both experiments on the diabetic the heat production rose somewhat in the first two-hour periods. This rise is perhaps to be referred to the increased work of digestion.

The manifestations on the part of the **vegetative nervous system** in diabetics has only recently been made the subject of study. I have already in the discussion of the experimental physiology mentioned *Löwi's* reaction. Its absence shows an increased excitability of the dilator pupillæ (innervated by the sympathetic). We have tested this reaction in human diabetes on a large amount of material and have found it positive in a number of cases. We could not demonstrate that it is connected with the intensity of the glycosuria or ketonuria. We sometimes found it positive in cases in an aglycosuric condition, and in other severe cases; even in the presence of coma, it was negative. The glycosuric action of adrenalin in diabetes has been studied by *Newburgh*, *Nobel*, and *myself*. It was found that in cases in the aglycosuric state, adrenalin in almost all cases leads to a distinct increase in the elimination of sugar. On the contrary, in a certain number of these aglycosuric cases, the action was negative. There were among these cases that had to be regarded as severe, cases that only on the complete withdrawal of the carbohydrate and strong limitation of the albumin would be maintained sugar-free, and that on the administration of slight amounts of carbohydrates responded with glycosuria. These investigations show the independence of the nervous and alimentary factors at least in the aglycosuric state. An especially intense action of the adrenalin on the heart and vascular system in diabetes could not be shown. On the contrary, among the cases investigated were a number in which enormous adrenalin-diuresis supervened. Among the numerous nondiabetes cases on whom we tested the diuretic action of adrenalin, we never saw an action so intense. It is especially worthy of remark that among the diabetics who resisted so intensely, were also cases in an aglycosuric condition. *Therefore in many a diabetic the vessels of the kidneys are in an abnormally irritable state,* [a fact] which was not known before. I might take advantage of this opportunity to add some remarks concerning the *diuresis* in diabetes mellitus. Ordinarily we find a parallelism between the intensity of the elimination of sugar and the amount of the urine. It has been known for a long time that there are exceptions to this rule. There are cases in which a long period of increased diuresis precedes the occurrence of diuresis (*v. Noorden*). There are further cases in which, as *v. Noorden* likewise emphasizes, the polyuria outlasts the glycosuria for a long period. Then there are cases in which, in spite of high percentage of sugar, the amount of urine is very slight. *Naunyn* reports for example a case in which about 8–9 per cent. of sugar was excreted, with 2 liters of urine. In another case there was just as much sugar, and a specific gravity of 1040, with urine amounting to only 1200–1400 cc. We designate these cases diabetes decipiens. On the other hand there are cases with considerable polyuria with relatively little elimination of sugar, especially if the diabetes came as a result of head injury. *Naunyn* reports, indeed, a case of pure uncomplicated diabetes who constantly, with a diuresis of 5–6 liters eliminated only 1.2–2 per cent. of sugar. Hence the elimination of sugar is certainly not the only cause of the increased diuresis, and perhaps not the principal cause. According to the experiments previously mentioned the increased diuresis has its foundation in an especial sensitiveness of the kidney vessels to an irritant circulating in the blood. We can summarize the observation set forth in the statement that *in many cases of diabetes mellitus a heightened excitability of certain organs innervated by the sympathetic (dilator pupillæ, liver, kidney, etc.), may eventually also exist in the aglycosuric condition.*

The excitability of the *autonomous nerves* in diabetes mellitus is not diminished throughout. We have even in numerous experiments in the advanced stage of diabetes found strikingly intense actions of pilocarpine on the secretion of sweat and saliva. Also the miotic action of pilocarpine is very distinctly pronounced. That the diabetic glycosuria is not diminished by pilocarpine, is here mentioned because the fact again illustrates the independence of the nervous and alimentary factors. In advanced cases there are found many kinds of manifestations that perhaps may even point to a heightened irritability in many territories of the autonomous nervous system. We observed in almost all very severe cases high-grade obstipation, whose spastic nature was shown on the palpation of the sigmoid flexure and through the appearance of the stools. Up to the present I have not seen similar statements in the literature. Purgative measures are of service in such cases only when they are given in rather large doses, and then defecation is rather painful. Such patients prefer enemas to purgatives. The spastic nature of this obstipation is demonstrated too by the prompt action of a subcutaneous injection of atropine (1 mg.). On what ground there occurs the development of such a spastic obstipation is difficult to say; it can hardly be due to the lack of bread in the diet, as these cases on account of considerable ketonuria could not long have been kept on a carbohydrate-free diet, and the diet was in addition always very rich in cellulose (vegetables).

I would further mention here an observation which I have likewise not been able to find in the literature. We found in all severe cases of diabetes in which the examination was made, a relative or absolute increase in the *mononuclear cells* in the blood. As the total count of the leucocytes was always normal, there always existed, then, a relative and absolute diminution in the number of neutrophilic cells. It is possible that chemotactic influences lie at the basis of this. If we regard this as in connection with the spastic obstipation, we could consider it as the expression of a high tonus of the autonomous nerves.

I would not leave the description of the manifestations of the vegetative nervous system without mentioning a finding that probably belongs here. In investigations carried out together with *Newburgh* and *Nobel*, we found on the *administration of thyroidin* to nondiabetic individuals a reduction of the fall of blood-pressure from heart to periphery. Investigations on the blood-pressure in the brachial artery with *Riva-Rocci's* apparatus showed no change, while the investigation at the finger with *Gärtner's* instrument showed in many cases a distinct fall of the blood-pressure. In the diabetics we found, however, after the use of thyroidin a distinct, and in many cases, an appreciable increase in blood-pressure with both methods; this increase often outlasted the thyroidin medication for days. We could also observe this in cases in the aglycosuric condition. It is very well likely that this increase of blood-pressure is brought about through an enormously increased activity of the chromaffin tissue. If this is so, it must be assumed that *in diabetes there exists an enormously increased excitability of this organ or of the nervous centers regulating its activity.*

Also the *erethism of the vessels of the skin* speaks for an increased excitability of the vegetative nerves. The red face of the diabetic, lending as it does such a characteristic appearance to the advanced case, is well known. Also there mostly exists distinct dermographism. On exposure the skin often reddens to far over the trunk. It is known that the skin of the severe diabetic is often very dry on account of the severe draining of the body of its water, yet there do not rarely occur *sweats*, even in cases that show no manifestations of a complicating tuberculosis of the lungs.

Finally I would mention a group of diabetics in whom the conditions of hyperexcitability and hyperirritability of the sympathetic nervous system are still more prominent. These are for the most part diabetics in middle life, who overwork much and who in their occupations are exposed to great excitements and cares; also traumas may have been sustained. Psychic excitements are here an important factor in the influencing of the glycosuria. The blood-pressure is often raised not inappreciably, but in spite of this, traces of albumin are found only transitorily, and here and there is seen an entirely isolated cast. In such cases, adrenalin acted glycosuric in the aglycosuric state; the *Löwi's* reaction was positive. We may perhaps designate these cases as hypertonic diabetes.

As example I cite the following case:

*Observation LXIX.*—G. K., forty-eight years old, conductor; entrance into the first medical clinic on Sept. 6, 1912. In the year 1904 the patient suffered a train injury. In it he was thrown to the floor, and the right thigh was contused. In July, 1910, he fell from a wagon, and with the fall had the sensation as if something internal had torn. Since this time, always sensitiveness to pressure in this region, and very nervous. In 1911 unquenchable thirst with decrease of the previous appetite. The skin was dry, the potentia coeundi fell off very much. On entrance there was found 3.7 per cent. sugar and a distinctly positive acetone reaction. The sugar-elimination after the ingestion of 75 gm. of roll and a third of a liter of cream was about 80 gm. dextrose, the excretion of acetone was about 3 gm. On withdrawal of carbohydrates the sugar sank rapidly, the oat-meal treatment that was instituted brought about only traces of sugar, the acetone disappeared. The tolerance rose very quickly, so that after six weeks the patient bore 60 gm. roll, 30 gm. rice, and 60 gm. potato without excretion of sugar.

The amount of urine during the sugar-free period was also appreciably increased. Mostly there were values of 2000. At the beginning also values between 3000 and 4000. The specific gravity was raised only in the first days. Then it sank quickly to about 1010, and later showed great variations; it mostly lay low, around or lower than 1010, and temporarily would increase to 1020.

The patient was very excitable, the patellar reflexes were lively, the blood-pressure was high, varying according to measurements by the *Riva-Rocci* apparatus between 130 and 150. Correspondingly the arteries showed increased tension, but there were no signs of arteriosclerosis. The heart dulness was broadened to a slight extent toward the left. In the urine was found on repeated examinations at most minimal traces of albumin. No casts were found in the centrifugated fluid. *Löwi's* reaction was positive.

In the aglycosuric condition 1 mg. of adrenalin was injected many times. Regularly there occurred a not inappreciable elimination of sugar, once to 6 gm., in the hours after the injection. One of these experiments took place at the time that the tolerance of the patient was already essentially increased. Further the diuretic action and especially the action on the heart and vessels was strongly marked. In the experiment mentioned the blood-pressure rose to 180.

The investigation of the respiratory gas-exchange (*Dr. Bernstein*) always showed normal $CO_2$ production, and mostly an increased $O_2$ consumption. The gas-exchange after an adrenalin injection was investigated twice. Both times the oxygen consumption and carbonic-acid production rose strongly, but the respiratory quotient was not influenced. I cite the following experiment as an example:

| | $CO_2$ | Per kg. per min. | $O_2$ | Per kg. per min. | RQ |
|---|---|---|---|---|---|
| Before | 217.6 | 2.75 | 317.7 | 4.02 | 0.685 |
| 20 min. after injection of 1 mg. adrenalin | 250.0 | ................ | 372.5 | ................ | 0.671 |

In this experiment the injection led to an elimination of 6 gm. of sugar. The action of adrenalin was therefore intensive in all respects, only the raising of the respiratory quotient was wanting.

I would here mention quite briefly the *complications* of diabetes mellitus. In diabetes in men, impotence is one of the most frequent complications, only very rarely does there occur increased sexual desire. With the former is often found an atrophy of the testicles. In the diabetic women, menstruation is disturbed only in the severest cases, but on the contrary, conception is rare. In men, there is never observed a retrogression of the secondary sexual characters. The deleterious influence affects therefore only the generative part of the function of the sexual glands. The vulnerability of the tissues, the falling out of the teeth, the suppurations, diabetic cataract, the furunculosis, the xanthelasma, the pruritus, the rheumatoid pains, the diminution of the reflexes, and the degenerations of the posterior column are here merely briefly indicated. These symptoms are for the most part brought into a relation of cause and effect with the constant hyperglycemia, yet this explanation is for very many of the cases as yet very uncertain. This is also true for the premature arteriosclerosis of the diabetic with its sequel, diabetic gangrene, which is perhaps the result of the hypertonic condition we have described.

Let us survey now the alterations of the metabolism in genuine diabetes! First, I would again point out that according to investigations up to the present there are demonstrable neither an increase of the albumin decomposition nor an increase of heat production. Why then does a severe case of diabetes become thin? The basis lies apparently in the devaluation of his diet through the limitation of sugar and of ketone-bodies. This is especially true of the omnivorous, irrationally fed, severe diabetic. Such a person loses flesh in spite of the abundant ingestion of the food because a certain part of the material ingested leaves the body unused. In such an individual the heat production can be raised at most by the increased work of digestion, and because he must warm the large amounts of fluids of which he partakes to body temperature. The polyuria conditions a slight loss of heat. This is however an *ectogenous* raising of the heat production. In the light and the moderately severe diabetic, he who can be made sugar-free very early by a relatively slight restriction of the ingestion of albumin and carbohydrate and thus again uses his diet to its full value, there lies no basis for emaciation. The severe diabetic can only be made sugar-free through great limitation of the albumins and carbohydrates. Also this individual may, as *Weintraud* has already shown, be maintained at body weight for a long time, on this just adequate diet, indeed it seems as though through the chronic underfeeding he may become established on a lower requirement for calories, as we can observe also in chronically underfed nondiabetic individuals. In still further advanced stages of the disease, the adequate diet does not serve any longer to maintain freedom from sugar in the urine; indeed in very severe cases it is no longer possible to limit the glycosuria to a low figure, as now on account of the strong formation of ketone bodies, carbohydrates must be administered unconditionally. That in such cases the carbohydrates are in a position to limit the formation of ketone bodies, at least to some degree, indicates that a part of the carbohydrates goes over the glycogen stage, although on account of the rapid re-combination this cannot be demonstrated with certainty in respiration experiments. The most marked effects are in such cases produced by the *exclusive* administration of carbohydrates, especially of oat-meal (*v. Noorden*), perhaps because the simultaneous administration of albumin favors the re-combination of the formed glycogen. In such cases, too, we then see the body weight rapidly increase, a phenomenon that is certainly not explained by the above by the inhibition of water. In the very highly advanced cases these carbohydrate treatments are, as is known, also of no use. The severe diabetic loses weight and uses up his albuminous constituent, because he can be maintained sugar-free and ketone body free only on an extremely just adequate diet; as soon however as the diet becomes more abundant, the elimination of sugar and ketone bodies is increased, by which the value of the diet is detracted from. That the fattening of severe diabetics presents great difficulties is intelligible as it is known that a fattening is only possible when abundant assimilation of carbohydrates goes on at the same time.

To me it seems that very much seems to speak for the fact that the metabolic disturbance that is present in genuine diabetes mellitus is made up of two different factors. The one factor consists of a disturbance in *anabolism*. This disturbance in the building up of glycogen is usually first to appear. The alimentary influence is here predominant. In the initial stages a disturbance becomes manifest only on overstraining of the carbohydrate assimilation. If we adopt the viewpoint that the disturbance of glycogenesis affects both liver and muscle and that combustion of the carbohydrates in the muscles is only possible after preceding assimilation, we may in this sense speak also of a disturbance in sugar-combustion. On account of the lessened formation of glycogen, there gradually develops a deficient splitting up of albumin and fat, and the formation of ketone bodies.

The other factor consists in a disturbance of *catabolism*. This occurs the most evidently, when in spite of the ruling out of alimentary influences sugar is continually formed from albuminous and fatty substances and eliminated (increased sugar-production). This increase of the catabolism must therefore be regarded as endogenous; it leads, if the lack cannot longer be made up through ingestion of food, to a melting down of albuminous and fatty substance. *We can therefore very well speak of an increased exchange in severe diabetics*, whether this is due to the devaluation of the food administered in excess, or to a melting down of the body substance. *This increased transformation is expressed in the experiments on respiration only by increased oxygen requirements not by increased carbonic acid production or heat production.*

These two disturbances show a certain independence of each other; in the initial stages of diabetes the disturbance in anabolism tends to come to the front, as the predominance of the alimentary factor would indicate. There do, however, exist cases in which the catabolic factor predominates already at the commencement (neurogenic diabetes). In the later stages both factors are present at the same time, although they are not always just as strong as each other.

If we review once more the alterations of metabolism that characterize the diabetes after extirpation of the pancreas, and compare these with those of genuine human diabetes, it is not hard to recognize a distinct difference; to both are common the anabolic as well as the catabolic disturbances. They differ from each other, however, in the behavior of the albumin exchange and the heat production. In the dog with pancreatic diabetes the decomposition of albumin and the heat-production are much increased; in genuine diabetes these are not essentially altered. Before we discuss this fundamental difference, I must first tell about the results of pathologico-anatomical research in genuine diabetes.

## Pathological Anatomy of Diabetes Mellitus

*Bouchardat* first in 1845 expressed the opinion that diabetes came about through a disease of the pancreas, at all events *Bouchardat* was forced to the assumption that under circumstances only a functional disturbance may exist, as in many cases of diabetes mellitus he found the pancreas normal.

After *Bouchardat*, *Lapirre*, *Frerchs*, *Cantani*, *Seegan*, and *Lanceraux* drew attention to the pancreas in autopsies on diabetics, and found that in addition to cases with the most varied alterations of the pancreas there were also cases of diabéte maigre in which the pancreas was apparently normal. In 1891 *Lemoine* and *Launois* described the sclerosis of the blood and lymph vessels in diabetes. In 1893 *Laguesse* first expressed the view that in diabetes the islands of *Langerhans* were diseased. In 1894 *v. Hansëmann* described a specific atrophy of the glandular parenchyma in diabetes mellitus, associated with proliferation of the connective tissue about the acini, which, on account of the similarity to granular atrophy of the kidney he designated granular atrophy of the pancreas. In a later work *v. Hanse-*

*mann* reported on investigations in thirty-four cases of diabetes mellitus. In the majority of these this granular atrophy was found, in six cases was found hyaline degeneration of numerous islands, to which, however, *v. Hansemann* attributed no great significance. *Dieckhoff* examined the islands especially and among seven cases found three times diminution in the number of islands, once disappearance of the islands, once the insular tissue qualitatively altered, and twice no alterations. Also he found that the glandular parenchyma for the most part showed changes. In 1898 *Schlesinger* first reported that he found in cases of pancreatic disease without diabetes that the islands were remarkably well preserved. In several interesting studies, *Opie* advocated the opinion that the disease of the islands of *Langerhans* was the cause of the diabetes.

*Opie* distinguished two types of chronic inflammation of the pancreas; an interlobar pancreatitis (twenty-one cases) brought about by occlusion of the excretory duct by pancreatic or gall-stone, or by compression of the same by tumors, or as the result of an acute inflammation of the pancreas on account of infection of it from the intestine, or by generalized tuberculosis, or as an accompaniment of atrophic cirrhosis of the liver. Here the islands are only a little altered, and indeed only altered if the cirrhosis is of a very high degree. On the contrary we find in interacinous pancreatitis the islands markedly affected and on marked changes in these also, for the most part, diabetes. *Opie* describes among the cases here observed also one of generalized hyaline degeneration of the islands of *Langerhans*. *Ssobolew*, into a consideration of whose experimental studies I have already entered, described alterations of the pancreas without diabetes in which the glandular parenchyma was in part highly altered, while the islands seemed to be very much more resistant. In primary or metastatic carcinoma of the pancreas the islands are often retained in the midst of the tumor tissue; only in one case of primary tuberculosis of the pancreas were traces of sugar present, there being present in this case also an extensive dense formation. In sixteen cases of diabetes he found, on the contrary, mostly disappearance of the islands or diminution of their numbers, or signs of degeneration. He comes to the conclusion that in diabetes, the islands seem to be the least resistant. As enemies of the insular theory appeared *Gutmann*, *Karakascheff*, *Herxheimer*, and others. *Herxheimer* found in a majority of these cases *v. Hansemann's* granular atrophy, and in addition in five cases found changes with the strong predominance of the regenerative new formation of excretory ducts, and he designates this form cirrhosis of the pancreas on account of its similarity to cirrhosis of the liver. He did not regard as significant the changes he found in the islands. Also *Schmidt* maintains a sceptical attitude. These authors show that in diabetes mellitus also the glandular parenchyma may be very much diseased, and that the islands throughout do not have to be the only part diseased; in many cases the islands are remarkably well preserved or show distinct signs of regeneration; and in many cases they appear entirely normal. *Karakascheff* upholds, as already mentioned previously, the opinion that the islands constitute only reserve material, and under circumstances can form new glandular parenchyma, while *Gutmann* assumes a new formation of islands from glandular parenchyma. *MacCallum* describes a case of *juvenile* diabetes in a child, in which the islands showed a high-grade hypertrophy. Before the appearance of a part of the work directed against the insular theory, *Sauerbeck* had treated the subject in a "Referat" and in a monograph. He collected one hundred and fifty-seven of diabetes from the literature. The islands found normal in 40 per cent. of which there were twenty-six cases with alterations of the glandular parenchyma. Changes in the islands were noted in one hundred and seventeen cases. In these the islands were not found at all, or only scars marked their places in seven. In twelve more cases the number of the islands was diminished whereby the glandular parenchyma was rendered in part atrophic. In ninety-eight cases the islands were altered qualitatively, there occurring hemorrhages, simple atrophy, hyaline or fatty or hydropic degeneration, sclerosis or acute or chronic inflammatory alterations. In seventeen of his own cases of diabetes mellitus *Sauerbeck* found mostly that alterations of the glandular parenchyma ran parallel with those of the islands, and indeed mostly that in severe cases of diabetes mellitus also distinct alterations of the islands were present. *Sauerbeck* inclines more to the insular theory; he believes that diabetes cannot originate from the parenchyma, as in cases of severe alterations of the parenchyma the diabetes may remain absent entirely.

Recent times have brought a series of important studies on this subject. *v. Halasz* investigated twenty-nine cases of diabetes mellitus. He found 90–95 per cent. of the islands normal eight times; six times in 60–90 per cent. of the islands, seven times in 30–40 per cent. of the islands, he found alterations that consisted in hemorrhages, sclerosis, atrophy, hyaline degeneration and in atheroma of the blood-vessels. Signs of regeneration were found only twice. Alteration of the parenchyma was found by *Halasz* chiefly in old diabetics, and the weight of the pancreas was for the most diminished, often distinctly. *v. Halasz* comes to the conclusion that not every diabetes is a pancreatic diabetes. *Heiberg* investigated six cases of diabetes mellitus and found the islands either qualitatively altered or the number of them diminished. *Heiberg* attributes this defect in the islands to their destruction by inflammatory processes, in which residues of the inflammation not always were necessarily present. In one case the islands showed in part the round-cell infiltration described by *M. B. Schmidt*, *Halasz*, and *Cecil Russell*. There was found in addition in this case islands with necrotic cells, without [round cell] infiltration; *Heiberg* regards these alterations as the later stage of the inflammatory processes.

In a later publication in which *Heiberg* reports on investigations of the pancreases of two diabetic children, he again mentions that the number of the islands must be considered as well as their quality. *Saltykow* examined twenty-one cases with pathologically altered pancreas without diabetes; of these four cases show insignificant alterations in the islands, which were otherwise well preserved. In many cases, especially in sclerosis and diffuse carcinomatous infiltration of the pancreas, the islands were indeed very well preserved. In nine cases of diabetes *Saltykow* found always alterations in the islands. Among these was a case of isolated hyaline degeneration of the insular apparatus with diabetes, as it had already been described by *Opie*, *Wright* and *Joslin*, and *others*.

A far-reaching confirmation of *Opie's* findings was contributed by *Russel L. Cecil;* he found among ninety cases of diabetes alterations of the pancreas in seven, and among these regularly alterations of the islands, such as sclerosis, hyaline degeneration, leucocytic infiltration. In seventy-six cases were found fibrosis, in twenty-seven hyaline degeneration, etc. In twelve cases the alterations affected the islands exclusively; and among the cases without qualitative alteration of the pancreas was found striking smallness of the organs or decreased number of islands.

The question has been studied the most thoroughly by *Weichselbaum*. *Weichselbaum* had previously reported with *Stangl* thirty-three cases of diabetes mellitus in which striking alterations in the islands, but not essential changes in the parenchyma had been found. The latest communication of *Weichselbaum* is based on the whole on one hundred and eighty-three cases of diabetes mellitus. The number of control experiments and pancreas of nondiabetics is still greater. Microscopically the pancreases of diabetics often showed distinct atrophy and decrease in size, and fatty degeneration; often they were entirely normal. Microscopically constant alterations in the islands were found. In addition to diminution in the number of islands and decrease of their extent (*Neumann*), *Weichselbaum* described a hydropic degeneration of the island cells; in this the protoplasm of the cells loses its structure, becomes transparent, shows characteristic granular inclusions and eventually are decreased in size (transition into atrophy). This hydropic degeneration was found in 53 per cent. of the cases and indeed almost exclusively in younger individuals. In 43 per cent. of the cases, mostly in persons over fifty years of age, *Weichselbaum* found sclerosis of the islands, proliferation of the connective tissue in and about the islands, and mostly interlobar and intralobar proliferation. There was found also sclerosis of the arteries. In 28 per cent. of the cases there was found finally hyaline degeneration of the island cells together with the sclerosis above mentioned. Manifestations of regeneration of the islands were found chiefly in the head of the pancreas, and indeed in young individuals. Hypertrophy of the islands were found only in some cases of insular sclerosis. While therefore the insular apparatus regularly showed alterations, high-grade degeneration of the glandular parenchyma was found only in closure of the pancreatic duct or in carcinoma of the pancreas. In the control investigations on the pancreases of non-diabetic individuals these changes were almost always absent, but on the contrary there existed high-grade atrophy of the glandular parenchyma, whereby the weight of the pancreas was very much diminished; in chronic tuberculosis even to 20 gm. *Weichselbaum* mentions that in diabetes mellitus the relation between regeneration and destruction of the islands must be considered; and not only the structure but also the number of islands.

On the basis of his investigations *Weichselbaum* distinguished from the pathologico-anatomical standpoint three forms of human diabetes; first a youthful form, the proper diabète maigre, in which is found the hydropic degeneration of the islands; this is hereditary and would seem to depend on congenital weakness or on failure of formation of the insular apparatus. Then he distinguished the form dependent on chronic interstitial pancreatitis, that occurs in the later years of life and is commonly associated with lipomatosis of the pancreas and general adiposis (diabète gras). This form is hence lipogenous or depends on a chronic catarrh of the excretory ducts and chronic alcoholism and is often complicated with cirrhosis of the liver. Finally the third form, which, depending on the hyaline degeneration of the islands, occurs in the later years of life, apparently is a subvariety of the second form, and is usually associated with sclerosis of the arteries.

I have reproduced rather in detail the numerous labors as to the pathological anatomy of the pancreas in "genuine diabetes," and have purposely confined myself strictly to the words of the various authors, because it seemed to me that an intimate penetration into the development of the question makes essentially more easy its solution. On reviewing once again the entire material detailed, we see that with increasing exactness the microscopical investigation and also the findings of the pathologico-anatomical alterations in the islands have become essentially commoner, so that the later authors almost all belong to the adherents of the insular theory. It is further perfectly clear that pathologico-anatomical alterations found in so-called genuine diabetes mellitus are not of a uniform nature, a conception that is upheld in the larger and more thorough of the works cited. A large group possesses well-defined characteristics, although the names given to it by different authors are different. It is the form of interacinous pancreatitis occurring in later life, that *v. Hansemann* calls granular atrophy of the pancreas, *Opie*, interacinous sclerosis, *Lepine*, and *Lemoine* and *Launois*, sclerose periacineuse, and which *Weichselbaum* regards as dependent on interstitial pancreatitis. The causes of it are probably very different. In part they are sclerotic changes similar to those of cirrhosis of the liver, often occurring in common with hepatic cirrhosis and like it dependent on alcoholism. Commonly the cause can be ascribed to high-grade arteriosclerosis of the vessels of the pancreas, in other cases an ascending catarrh of the duct system might be the cause. The latter cases go over without sharp boundary into that large group of high-grade atrophies of the pancreas, which we previously treated under the gross anatomical alterations of the pancreas. In all these cases are found in addition to changes in the insular apparatus more or less pronounced alterations of the glandular acini, which is true of the cases that proceed from catarrhs of the excretory ducts only when the process is more advanced. It is comprehensible why these cases do not lead to absorptive disturbances, for there is still enough functionating parenchyma present, and it is to be expected that such disturbances became manifest only on high-grade diminution of pancreatic juice production. The decision as to whether the alterations in the insular apparatus observed in this form suffice to explain the disturbance in carbohydrate metabolism is certainly very difficult, and is further complicated by the occurrence, commonly observed, of regenerative manifestations in the islands. It is indeed very questionable whether these new-formed islands have the same functional integrity. We see, however, in many forms of cirrhosis of the liver often strongly developed and widespread regeneration of the liver tissue, and yet we find in these cases signs of deficiency of liver function. Also the occurrence of individual hypertrophic islands and adenomatous proliferations of islands does not furnish a certain conclusion as to the function of the entire insular apparatus. Likewise, as *Saltykow* points out, just as little does the finding of partially normal islands speak against the island theory; for example, we have in cases of nephritis, large amounts of normal renal parenchyma visible microscopically, without casting doubt as to the insufficiency of the renal tissue. That also in this group are found cases in which the insular apparatus has suffered relatively severe damage need cause no wonderment. *Weichselbaum* emphasizes the fact that the cases with isolated hyaline sclerosis of the insular apparatus probably form only a subdivision of this group; also here is commonly found a sclerosis of the vessels of the organ; it seems to me very likely, however, that in these cases of isolated sclerosis of the insular apparatus there is expressed a certain undervaluation in the rudiments of the insular apparatus, that becomes manifest only on the additional occurrence of further damaging influences.

For the judgment of the rôle that the pancreas plays in the pathogenesis of diabetes mellitus, no doubt the second group—that which affects youthful individuals—is the more significant. Most important for us are those cases in which the diabetes commences at an early age, and, ceaselessly progressing, leads to fatal coma. It is these cases that up to the present have further so unsatisfactory pathologico-anatomical findings. The monographs on diabetes by *Naunyn* and by *von Noorden* state likewise that in the rich experience of these authors numerous cases are met with, in which even the most careful microscopical examination of the pathological anatomists did not show anything certain. In one of these cases the count of the islands has furnished inferences worthy of remark. It is shown in this group that the number of islands and also their size is markedly diminished, and indeed there are statements that the islands are entirely wanting. The supposition of *Heiberg* that in such cases the defect in islands can be referred to a preceding inflammation with the formation of scars has much in its favor. In many cases of juvenile severe diabetes, however, the number and size of the islands is insignificantly and perhaps not even at all diminished. In these cases *Weichselbaum* constantly found the hydropic degeneration. This statement of *Weichselbaum's* has up to the present time not been recognized by all pathological anatomists. If, however, the hydropic degeneration in such cases is found to be constant, we must also ask the question if the alterations are not of a secondary nature, brought into existence by the long duration of the hyperglycemia and acidosis, and if these relatively slight alterations suffice to explain the high-grade functional deficiency. This form of diabetes always commences with heavy elimination of sugar. In the majority of cases there is found in the later stages an intensity of glycosuria, that comes up to that seen in pancreasless dogs, and in the most of cases even exceeds this. On the whole we can hardly be mistaken if we were always to asssume a participation of the pancreas in such cases. The hereditary element so conspicuous in the pathology of this form of diabetes points to a weakness in the "Anlage" of the insular apparatus, as a result of which any toxic or infectious deleterious influence at all finds a locus resistentiæ minoris. In spite of all this we cannot reconcile the incongruity of the pathologico-anatomical findings and the intensity of the metabolic disturbance and must ask ourselves the question whether if in this form of human diabetes, and perhaps in the most cases of severe human diabetes, there is not present, in addition to the insufficiency of the pancreas, also another disturbance that we have essentially to regard as an increase of sugar production dependent on a nervous basis.

Before we enter into this question, it is necessary to observe more carefully those forms of diabetes in which the clinical observation or the pathological anatomy points toward a prominent participation of the nervous system in the coming about of the diabetic disturbance of metabolism.

The question as to whether we are justified in recognizing a "nervous form" of diabetes has been discussed in a lively manner for a long time. The discovery of the "piqûre" happened before that of diabetes after extirpation of the pancreas. Since the time that the discovery of pancreatic diabetes turned the general attention toward the pancreas, the interest in nervous diabetes has fallen behind. The greater part of the clinical observations of "nervous" diabetes come from earlier times, thus making critical observations not less difficult.

I shall first select from the observations at hand those which seem to me the most important, and describe them more exactly.

Glycosuria occurs not infrequently in *brain-hemorrhages* and encephalomalacias. This was first described by *Leudet*. They may be associated with acute hemorrhages as well as the chronic encephalomalacias. A case of the latter sort is described by *Naunyn* in which the diabetes gradually developed during a slowly progressing encephalomalacia. For the most part there exists in addition to the glycosuria, polyuria, and also even albuminuria. Cases of the first kind are communicated by *Dutrait*, *Frerichs*, and *others*. The seat of the hemorrhage or softening in such cases associated with glycosuria is mostly the pons or its vicinity. Especially interesting is the case of *Reinhold*. In a sixty-three and one-half-year-old woman with melancholia, ten days before death there developed a marked edema of the feet and strong glycosuria. Section showed a hemorrhage on the floor of the fourth ventricle (serial sections), slight hydrocephalus, and a strong hyperemia of the liver. It should not remain unmentioned that glycosuria is sometimes observed in the parts of the brain that lie further off, and that cases occur in which there is no glycosuria in spite of hemorrhages in the neighborhood of the pons. Such a case is reported by *Lemcke*. In this case there was an enormous lowering of the body temperature to 23° C. There was found neither glycosuria nor albuminuria. Section showed a fresh focus of hemorrhage beneath the floor of the fourth ventricle.

It is an interesting fact that *H. Strauss* in tests for alimentary glycosuria in cases with fresh apoplectic attack, several times found them positive immediately after the attacks but they were negative later. In this category belong too the cases of brain hemorrhage after trauma to the head. The first case was described by *Claude Bernard* (Physiol. expérim., Tom. 1, 1855). Glycosuria disappears at the same time as does the wound.

Here also belongs the case of *Drummond*. A seventy-six-year-old man suffered a blow on the head. Since that time increasing weakness, thirst, and glycosuria. Autopsy showed besides an extreme dilatation of the lateral ventricle and the aqueduct of *Sylvius*, a small blood effusion in the fourth ventricle.

I mention further the case of *Kämmitz*. A seventeen-year-old girl, previously well, caught her head in a cutting machine. Loss of consciousness, later vomiting, and copious bleeding from the nose, and downflow of blood along the posterior wall of the pharynx pointed with certainty to fracture of the base of the skull. The temperature at first was 35° C. After two days an abducens paralysis became evident. A week after the trauma there developed increased thirst, polyuria, and glycosuria (about 1 per cent. sugar). The sugar-contents gradually rose to 2.3 per cent. There now existed excessive polyuria. About three weeks after the trauma the somnolent condition had disappeared, the diplopia still existed, and a unilateral hypoglossus paralysis had developed. During the next few weeks, the sugar following exclusive meat diet fell to 1 per cent., but the polyuria had decreased but little. Two months after the trauma traces of sugar were still present, one month later the urine in spite of abundant ingestion of food was entirely free of sugar, but there still existed a diuresis of 4–6 liters, with a specific gravity of 1005. Nothing was noted, more's the pity, as to the further course. The supposition of a hemorrhage in the medulla oblongata, that became still more marked some time after the trauma, is very probable in this case.

Entirely similar is the case of *Plagge*. A sixteen-year-old boy suffered a head injury, after which amblyopia and strong glycosuria commenced. The glycosuria disappeared after two or three weeks, while the polyuria remained for two or three months.

Further I might still mention the case of *Loeb*. In the first case (pontile hemorrhage with rupture into the fourth ventricle and with general arteriosclerosis) sugar and albumin were found in the urine. The urine had been examined previously and found to be free of sugar. In the second case there occurred after an apoplexy (probably small hemorrhage of the pons) sugar and albumin in the urine. All manifestations later vanished leaving not a trace behind. *Loeb* regards the albuminuria as conditioned centrally.

In addition to the hemorrhages, it is chiefly *tumors* and *abscesses* in this region that can lead to glycosuria. The case of *Iwan Michael* is much cited. In a twenty-five-year-old man there occurred, together with increasing weakness and tormenting headache, polyuria, polydipsia, and glycosuria. The amount of urine reached over 6100 cubic centimeters, the elimination of sugar reached to 25 gm. Death in coma followed later. Autopsy showed a cysticercus racemosus of the floor of the fourth ventricle. *Steida* reports on the contrary a case of cysticercus racemosus of the fourth ventricle which, in spite of changes in the floor of the ventricle, did not call forth glycosuria.

Of the other changes in the floor of the fourth ventricle associated with glycosuria have been observed *tubercle* (*de Jonge*) *sclerosis*, *abscesses* and *tumors* (especially gliomata). The changes may also affect the vicinity of the cerebellum. The first glioma was reported by *Nevrat-Perrotton;* other cases are described by *Reimer*, *Catola* and *others*. Especially worthy of remark is the case of *van Ordt*. It concerned an eight-and-one-half-year-old girl in whom no sugar was found at the beginning of the illness. The test for alimentary glycosuria was first positive on the aggravation of the tumor symptoms, then 3½ per cent. of sugar occurred in the urine, then on limitation of the carbohydrates in the diet the sugar disappeared, later to reappear also on a strict diet to the extent of ½ per cent. The autopsy, in addition to showing several miliary tubercles on the floor of the fourth ventricle, revealed a tumor in the territory of the posterior corpora quadrigemina, the pes cerebri and the tegmentum of the pons that also involved the floor of the fourth ventricle. According to the judgment of *van Ordt*, this could have been present only in the course of the last weeks. The pancreas was found to be normal. According to *van Ordt's* statistics, glycosuria has been found up to the present in

| | |
|---|---|
| Cerebral tumors | 1 time |
| Cerebellar tumors | 1 time |
| Basal ganglionic tumors | —— |
| Thalamic tumors | 3 times |
| Tumors of the corpora quadrigemina | 3 times |
| Dorsal pontile tumors | 5 times |
| Basal pontile tumors | —— |
| Tumors of the floor of the fourth ventricle | 18 times |

If we take only those cases in which the floor of the fourth ventricle was destroyed to a greater or less extent, we find that 70 per cent. of all these cases are associated with glycosuria. Tests for alimentary glycosuria were found positive five times in eleven cases of tumors of the interior of the skull, three times in sixteen cases of other diseases of the brain (among them one case of lues). It should be mentioned that abscesses of the cerebellum very commonly lead to increase of temperature and glycosuria (*Hammond*).

I believe that among the cases detailed as well as among numerous analogous cases there are those which fulfill all the requisitions of a diabetes conditioned nervously. It is true, as *Naunyn* says, that he has seen many cases of apoplexy with glycosuria but that he could not exclude in these the possibility that a slight diabetes did not exist beforehand. It must further be said that exact examinations of the pancreas especially with reference to the insular apparatus are scarcely at hand. We can, however, only with difficulty conceive how in individuals with previously perfectly normal sugar-metabolism, and especially in the youthful cases, so high grade a damage to the pancreas can develop so suddenly. The parallelism in the development of the glycosuria and the brain symptoms points much the more to the fact that alterations in the nervous system have a decisive significance. According to the experimental experience up to the present only the assumption of an *irritation* of the nervous centers and paths as cause of the "nervous" glycosuria is possible. It is therefore intelligible that pathological alterations in the neighborhood of the floor of the ventricle or the subthalamic region do not always necessarily lead to glycosuria. Irritation would the sooner follow if tumors or apoplexies gradually encroach upon the corresponding centers; rapid destruction of these centers on account of hemorrhage or softening would much rather lead to symptoms that are the opposite of irritative symptoms. The case of *Lemcke* with considerable hypothermia may be perhaps explained in the above way. I should like to point out one point further, namely, the strong hyperemia of the liver in *Reinhold's* case, which is seen regularly too after the piqûre.

The cases of diabetes after *trauma* here need a more exact analysis. We have to consider the following points:

1. Whether the diabetes began immediately or at least a short time after the trauma, or after an interval of several months or years.

2. Whether the trauma affected the head and whether other brain symptoms existed in addition to the glycosuria, or whether other parts of the body were affected by the trauma.

3. Whether the diabetes healed again, or whether it existed further or relapsed; in short, whether a chronic diabetes developed.

Concerning the frequency of these different factors several statistics are at hand. *Jodry* (cited by *Lépine*) collected one hundred and forty-five cases of diabetes after trauma. The trauma affected the head in seventy-two cases—50 per cent.; the vertebral column in twenty-seven cases—20 per cent.; the abdomen in twelve cases—8 per cent.; the seat of the trauma was not defined in 1.7 per cent.

In a third of the cases, the diabetes became manifest during the first days after the trauma.

*Lépine* analyzed twenty-nine well observed cases from the literature and added five cases of his own. The symptoms of diabetes appeared in the first three days—ten times; in the first week—five times; in the first three months—twelve times; later seven times.

*Asher* found among one hundred and twenty-nine cases of diabetes after trauma fifty-four cases of injuries of the head; sixty-two cases of injuries of other parts of the body; nine cases after injuries of an undefined kind.

*Higgins* and *Ogden* among two hundred and twelve cases of head-injury, found sugar in 9.3 per cent. If only the severest cases were considered, the percentage rose to 23.4 per cent.

Among eighty-four cases of simple wound of the scalp, sugar was found in 5.95 per cent.

Among forty-three cases of wounds of the scalp that laid bare [freilegten] the bone, in 9.3 per cent.

Among forty cases of concussion of the brain with loss of consciousness, but without fracture, in 2.5 per cent.

Among twenty-four cases with fracture of the vault of the skull, in 20.8 per cent.

Among twenty-one cases with fracture of the base of the skull in 23.8 per cent.

The question as to the connection between trauma and diabetes has been discussed in a lively manner. *Ebstein* and later *Kausch* collected the cases of traumatic diabetes from the literature. While *Ebstein* inclines to the view that also cases of chronic diabetes, eventually diabetes first occurring a long time after the trauma may be ascribed to the trauma, *Kausch* is very sceptical. He would hold as valid only the ephemeral or transitory glycosurias occurring immediately after, or only a short time after the trauma, and denies the connection between trauma and chronic diabetes, especially when the latter first occurs a long time after [the accident]. I believe that we must consider *Kausch* right in many points, even if perhaps he goes too far, in the separation of the ephemeral or transitory glycosurias and chronic diabetes. It seems to me appropriate to go a little further into the points [just] previously sketched. I am not regarding the responsibility serving for the law for accidents. *Naunyn* and *v. Noorden* mention that one must not be too narrow minded, as with the obscurity of the conditions, single individuals should not suffer harm on account of theoretical considerations. The scientific side of the question, however, demands a much stricter criticism.

Now as regards what concerns the first point, we can ascribe, with considerable justification diabetes after head injury to the injuries of the nervous centers regulating sugar-metabolism, when the elimination of sugar occurs within the first eight to fourteen days and especially when, too, other symptoms are present that indicate an injury to the brain stem and medulla oblongata. I have mentioned in brief several such cases on page 553. As further examples I would cite both cases of *Bouchard*. In a seventeen-year-old and twenty-one-year-old man respectively there occurred, after fracture of the base of the skull glycosuria to 1.5 per cent. and 1.75 per cent., and albuminuria and cylindruria. The first case healed entirely, but the second case died after some days. If no brain symptoms are otherwise present, we cannot, however, deny without anything further the connection with the trauma. Very interesting is the observation of *Höniger* that new-born infants whose heads have been strongly squeezed by the artificially induced birth, can show glycosuria for several days, while the long duration of a spontaneous birth never leads in itself to glycosuria.

If the glycosuria starts in a longer time after the trauma, we can here also not deny the connection with trauma in every case without anything further. It is conceivable that blood effusions that are undergoing absorption in organization, may exercise an irritation in the corresponding centers through shrinkage and the action of traction (*Rosenberger*). Of course this would hold only for very few cases. We may regard that of *Schaper* as such a one. In a duel, a dagger thrust penetrated the orbit and went deep into the cranial cavity. There developed a right-sided paralysis and gradually a high-grade diabetes. Death occurred after three and a half months; it was found that the path of the stab reached to the left border of the medulla oblongata and was filled with pus and coagulated blood. There should finally still be thought of, in such cases of later glycosuria, the spontaneous glycosuria of the traumatic neurosis. We shall consider this latter in the discussion of the connection of psychoses or psychic excitements with glycosuria. For the question whether we are allowed to bring the glycosuria that occurs late into connection with the trauma, is the existence of polyuria full of significance. In many cases of head injury the glycosuria starts in simultaneously with pronounced polyuria. Usually both develop at the same time. If the glycosuria later disappears, the polyuria often lasts for many months, in other cases the polyuria develops first, and the glycosuria accompanies it only after weeks or even months. The central origin of such polyuria is very probable. On it is based the hypothesis of a central origin of the glycosuria. In any case the similarity with the sugar and polyuria puncture is worthy of notice.

The second question concerns itself with whether glycosurias after trauma that does not affect the head, but other parts of the body, can be referred to the trauma and can be regarded as nervous glycosurias. *Krausch* himself has furnished noteworthy contributions to this subject. He described twelve cases of fractures of the pelvis, thigh, leg, patella, or toes, that showed ephemeral glycosuria. This glycosuria continued for at most ten days and under circumstances, on the ingestion of grape-sugar, would be increased to 30 gm. It is worthy of remark that these cases later did not show any alimentary glycosurias and therefore presented an entirely normal carbohydrate metabolism. Before *Kausch*, *Haedke* has already pointed out that after traumata of different kinds alimentary glycosurias would be obtained in a large percentage. The connection of such transitory glycosurias with trauma, in cases that are not narcotized, is doubtless. Experimental pathology (glycosuria after injury to the sciatic, etc.) gives us an idea as to the kind of connection. Very much severer is the significance in a series of cases, of which I shall quote the following cases of *Scheuplein* more exactly.

A young soldier who was not hereditarily predisposed to diabetes fell about 12 meters from a third-story window. He fell on his buttocks. There was found a luxation of the first lumbar vertebra, without there being symptoms that pointed to an injury of the spinal cord. Reposition was successful; complete cure resulted, so that later the patient could again ride and carry on severe bodily labor as menial servant [in the army]. Fourteen days after the fall it occurred that the urine was much thinned and pale, and that the feeling of thirst was distinctly increased. The urine contained sugar. Ten days later the sugar-content of the urine was very great, and the amount of urine reached about 13 liters. The patient was placed on a meat diet. After fourteen days the sugar had disappeared, but the polyuria remained for a while longer. Two years after the trauma the patient was entirely free of sugar, although his diet consisted chiefly of cereals. The body weight, that at the time of the sugar elimination had sunk very low, raised again so that in short the patient could be regarded as cured in every respect. The significance of this case is indeed not easy [to determine]. We could perhaps think of an apoplexy of the pancreas, but against this speaks the simultaneous diabetes insipidus. Against a hemorrhage in the medulla oblongata speaks the absence of any other brain symptoms. *Scheuplein* discussed the possibility of an injury of the solar ganglion. To me the possibility seems in any case to be thought of that on account of the great swelling formed by the injured vertebra there followed an irritation of the sympathetic paths in their course from the sugar center to the suprarenals. By this means can be explained even the polyuria. *Scheuplein* also refers to a case of *Braun*. In a twelve-year-old boy there existed a spondylitis of the twelfth thoracic and first lumbar vertebræ with an acute-angled kyphosis. When the boy was placed in a horizontal position, symptoms of collapse, with polyuria and glycosuria, developed. Comfortable lying on roll pillows brought about a cessation of all manifestations. Also I must not leave unmentioned the case of *Schwenkendick*. A man sustained a tread of a foot in the vicinity of the navel. After some hours great thirst and polyuria started. Two days afterward there occurred stormy manifestations, marked pallor of the face, coldness of the extremities, distention of the abdomen, frequent vomiting. The urine was at first free of albumin and sugar, after two days more there was found 4.75 per cent. of sugar and abundant acetone. Later the patient evacuated black stools that contained blood, and death soon followed under manifestations of coma. The author thinks of apoplexy of the pancreas or necrosis of the pancreas as an affection of the splanchnic nerves.

It is possible that in the setting free of this glycosuria, pain plays a considerable rôle. For instance, it has been known for a long time that in severe neuralgias there exists inclination to alimentary glycosuria. *Frerichs* reports such a case; in a forty-eight-year-old man there occurred, after a cataract operation, at the same time as severe neuralgic pains of the right half of the face, sugar in the urine up to 2½ per cent. As the pains ameliorated, the sugar disappeared and ten years later the man was still sugar-free. It is also known that cases of sciatica, especially those with frequent attacks, frequently show alimentary glycosuria. *H. Strauss* found [urines tested for alimentary glycosuria] in three cases positive, and then when the painful attacks were over, negative in the same patients. Much cited is also the case of *Frerichs*, concerning a shot injury of the sciatic nerve with severe attacks of pain, during which sugar always appeared in the urine. As the suffering ameliorated the sugar disappeared entirely. It might be possible that in such cases the irritation passes away along the sympathetic nervous system through irradiation. We do not know certainly as yet as to whether longer continuing glycosuria may originate through involvement of the splanchnics or the great ganglia of the sympathetic as the result of chronic inflammatory processes—impaction in hard tissue, hemorrhages, etc. In the cases of long continuing glycosurias of high grade known up to the present time, and previously detailed, the associated involvement of the pancreas or the centers in the brain stem through the violent concussion cannot be excluded entirely.

I now turn, finally, to the third question, whether in the wake of a trauma a chronic or eventually a later recurring diabetes on a nervous foundation, is conceivable. It seems to me that the possibility that a scar formation exercising irritation on the centers regulating sugar metabolism cannot entirely be ruled out, as I have already signified. But at all events severe diabetes of year-long duration, that is progressive and eventually ends in a coma, cannot be explained by it. If the diabetes after the trauma is chronic, it is indeed very probable that a predisposition [Anlage] for diabetes has existed beforehand.

Although we, in the previously detailed cases of organic alterations of the brain, must regard it as extremely unlikely that an acute alteration of the pancreas should exist at the same time, this (factor) cannot be excluded in those cases of *brain syphilis* which are also designated "nervous." The cases are so interesting that I would like to discuss them. In 1860, *Leudet* first described such a case. It was that of a thirty-two-year-old woman, who four years previously had progressed as far as the development of a "saddle nose." In her there developed rather suddenly polyuria and polydipsia, unconsciousness, paralysis of the eye-muscles, left-sided anesthesia, etc. In the urine was abundance of sugar. On the institution of a potassium iodide treatment the diabetes insipidus and glycosuria disappeared, and also the brain symptoms ameliorated. Later, with a more recent aggravation of the brain symptoms, polyuria occurred again, but not sugar. Autopsy showed that the choroid plexus was adherent to the left border of the calamus scriptorius, and the brain substance of this was "eroded." In the book by *Frerichs* are reported three cases of lues with brain symptoms and in part associated with very severe diabetes, in which diabetes disappeared under antiluetic treatment, or, as in one case, improved considerably. Very instructive cases are reported by *Dub* and *Lemonier.* I would like to mention more in detail the case of *Hemptenmacher.* In a forty-two-year-old woman who had been infected with syphilis thirteen years previous there developed, at the same time with a polydipsia and pollakisuria, a left-sided hemiplegia with severe headache. In the urine was found 3.6 per cent. of sugar. Under the inunction treatment and potassium iodide the glycosuria gradually disappeared without the retention of an antidiabetic régime. Also the brain symptoms gradually ameliorated, and later complete cure was obtained.

In this and in other cases there without doubt exists the casual connection between lues and diabetes. The occurrence of diabetes simultaneously with tertiary luetic symptoms, the cure of diabetes by antiluetic treatment without alteration of the diet alone allows of no other conclusion. On the other hand the interpretation of the condition as nervous diabetes is entirely uncertain, as a simultaneous alteration of the pancreas is not to be excluded. It is true that never was the occurrence of absorptive disturbances mentioned, but the fact cannot be excluded that the insular apparatus may alone have been damaged in its function; the case of *Manchot*, moreover, that ran along without brain symptoms showed likewise no absorptive disturbances.

## Theoretical Conclusive Considerations

Before I finally turn to the question as to what signification the internal secretion of the pancreas has for the pathogenesis of human diabetes, I should like briefly to summarize the most important points that were touched upon in the course of the exposition.

1. Embryology, anatomy, experimental pathology, and clinical observation point to a certain independence of the insular apparatus. The embryological investigations showed that the insular apparatus and the acini developed separately. The anatomical investigation showed a different structure of these two apparatus; a transition of the one tissue-element into the other has not up to the present been demonstrated with certainty. The experimental pathological investigations showed that after ligation of the excretory ducts the acini become destroyed, while the insular apparatus for the most part behaves refractorily. The pathological-anatomical observation likewise showed that on the one hand the insular apparatus ordinarily is more resistant to certain destructive processes and that on the other, isolated alterations of the insular apparatus occur; finally clinical observations showed that disturbances in the function of the glandular apparatus and the insular apparatus occur entirely apart from each other, and that to such isolated disturbances a corresponding pathological-anatomical finding can with probability be ascribed.

2. After the complete extirpation of the pancreas always occurs (in the dog) a characteristic disturbance of metabolism; there always develops a severe diabetes leading to death, in the course of which affection the glycogenesis is to a high degree, but not entirely, prevented in the liver and muscles; the disturbances in the assimilation of sugar might lead immediately to a disturbance in the combustion of sugar. In addition to this disturbance in anabolism exists a severe disturbance in catabolism, that affects not only the carbohydrate metabolism (increased sugar production), but also the albumin, fat, and salt, metabolism. The catabolic disturbance shows, on extirpation of the pancreas, great regularity; there further exists regularly a certain hyperexcitability of the sympathetic nerves.

3. The investigation of the metabolism in human diabetes shows disturbances in both anabolism and catabolism, the latter, however, confine themselves only to the sugar metabolism, while quantitatively increased breaking up of albumin and fat are not demonstrated even in the severer cases. On the contrary, catabolic disturbances in the sugar metabolism are much more severe in the graver cases, as the glycosuria attains a much greater intensity than in the dog without a pancreas.

4. Concerning the nervous manifestations in human diabetes, we can distinguish two types, between which we find all possible transitions. In the first, rarer, type, to which *v. Noorden* has lately directed attention, the ner-

vous manifestations are strongly in the foreground from the beginning. Before everything is the psychic factor, that under circumstances dominates the elimination of sugar from the beginning up to even years, or at least influences it to a marked degree. Especially accentuated does the nervous factor enter into certain psychoses, into traumatic neuroses, into severe attacks of pain, etc. But this can be the case in even uncomplicated cases of human diabetes. In such cases it would perhaps be possible to demonstrate regularly a hyperexcitability of a certain part of the sympathetic system; especially does the glycosuric action of adrenalin always seem in such cases to be distinctly present, indeed under circumstances the entire complex of adrenalin action (vascular and cardiac manifestations, etc.), seems to be very decidedly pronounced. There are all the transitions between this and hypertonic diabetes, in which in addition to the hyperexcitability of the sympathetic nervous system, there also occur conditions of permanent hyperexcitability.

In the much more frequent second type the alimentary factor is the foreground from the beginning. It governs the intensity of the elimination of the sugar, whereas psychical factors have no distinct influence on this. Especially are there no manifestations of hyperexcitability of the sympathetic system, especially that apparatus which has to do with the regulation of sugar metabolism. In the later stages of this type, when it has developed to severe diabetes, there occur a series of symptoms that point to a hyperexcitability of the sympathetic system. Then adrenalin can make the glycosuria distinctly more intense or, if the patient has been rendered sugar-free, may call forth glycosuria. Further there then begins an especial sensitiveness of the renal vessels, in that adrenalin, or similar agents, like pituitrin, then act diuretically. Finally there now shows itself the noteworthy phenomenon that long continued administration of thyroidin raises the blood-pressure, without eliciting any stronger manifestations of hyperthyroidism than when it is used in nondiabetic individuals. This phenomenon seems to indicate an especial lability of the sympathetic nervous system. To this is added in severe diabetes the known erethism of the vessels, the genesis of which is hard to account for; finally I would like to point out a symptom that seems to me to belong at this place; it is the extraordinary richness in blood of the liver, which we see, as already *Klebs* mentioned, in the individuals dead from severe diabetes.

All these manifestations are common to the later stages of both types; I would believe that they are more markedly pronounced in the later stages of the first type. Yet for the corroboration of this is necessary a greater material than has been observed up to the present.

Let us now investigate how far the pathologico-anatomical findings suffice to explain the clinical observations. No doubt there are cases with gross anatomical disturbances of the pancreas and especially of the insular apparatus, that without anything else explain a severe disturbance of function of the same. Such cases rightly deserve the name *pancreatogenic* diabetes. There are further described in detail cases of alterations of the central nervous system, whose seat makes appear intelligible long continuing irritative manifestations on the part of the sympathetic centers, that have to do with the regulation of metabolism, or perhaps on the part of the paths that bind these with the chromaffin tissue. It is doubtful whether a permanent diabetes may become manifest through such gross anatomical disturbances. In addition there exists a great many cases in which nothing certain is found in the nervous system and the insular apparatus shows only relatively slight alterations. Only if we accept the viewpoint of *Weichselbaum*, it seems to me that up to the present there has been in such cases an insufficient agreement between the pathologico-anatomical findings and the intensity and acuteness of the clinical manifestations. Especially would this hold true for the juvenile uncontrollably progressive cases of diabetes mellitus. In such cases there lies close the thought of a congenital weakness in the rudiment [Anlage] of the insular apparatus, whereby the hereditary and familial occurrence may become more intelligible. We can also suppose that in such individuals various deleterious influences—infections and intoxications, etc.—find a locus resistentiæ minoris and damage the insular apparatus; and we can further suppose that the same alterations of the insular apparatus may recuperate, especially if by reason of a corresponding dietetic treatment or prophylaxis the damaged organ is given time and rest for recovery.

It appears, however, that through these means of consideration alone the problem of human diabetes will not become solved. The nervous factor that, as clinical observation teaches, often occupies the foreground, assigns to the nervous system a much more important rôle. A disturbance of the regulation of sugar metabolism through the central nervous system is especially to be thought of in two directions. Either the activity of the insular apparatus may be deficient thereby, so that the nervous impulses necessary for a normal function are too weak—an insufficiency on a nervous basis, such as we know in the glands with an external secretion, for instance, in achylia gastrica. It appears to me, however, that according to that which I have previously set forth concerning the nervous type, this assumption a priori has little to recommend it. Or in the metabolism of sugar there may be an increase in catabolism through an enormous excitation of those centers which regulate the activity of the chromaffin tissue. We can designate this type, then, as *nervous* or *adrenalinogenic*. I would only point out especially that in this type the insular apparatus is entirely intact. That such an excitation of the nervous centers leads to a continuous and strong glycosuria, brings into relief a certain weakness of the insular apparatus. In individuals with completely normal pancreas, such excitations as increase the catabolic processes are neutralized by the corresponding counter-regulations. The difficult feature of the question seems much more to lie in the fact that in the nervous type this condition of hyperexcitability seems *to occur primarily* and that it increases the disturbance in metabolism in a manner that is hardly possible through failure of the insular apparatus alone, while it accompanies the pure pancreogenic type only *secondarily* and perhaps in a less intense form. That also in the nervous type an increased adrenalin-contents of the blood could not up to the present be demonstrated, seems to me to signify nothing against this assumption; on the one hand, the biological methods up to the present have been insufficient for the demonstration of adrenalin in the serum (I refer to the work of *O'Connor*, *Priestly*, *Fleming*, *Kahn* and *myself*) and on the other hand we can conceive that on insufficient contraregulation also minimal surplus production of adrenalin already produces a significant effect on sugar metabolism.

As to the cause of such an abnormal excitation in the nervous system we know as yet nothing. We have, however, met with similar conceptions in the diseases of the other ductless glands. I refer to Basedow's disease where especially in the peracute cases, the increase of function of the thyroid gland is ascribed by many authors to a central excitation; and indeed they regard many symptoms as coordinate with hyperthyroidism, and conditioned centrally. We could designate the entire disease picture as hyperthyrosis, and the important syndrome conditioned by the hyperfunction of the thyroid gland we could designate hyperthyroidism. According to this hypothesis we could regard these hyperfunctional conditions of the ductless glands as neuroses. So far as this theory of diabetes is concerned we are unmistakably approaching again the view first propounded by the first genial investigator of diabetes, *Claude Bernard*, although in a considerably modified form.

If we now on the basis of the developed view, finally turn to the question as to why the diabetes of dogs without their pancreas deviates in some essential points from that of the genuine human diabetic it seems to be that as yet a satisfactory explanation has not been possible. The principal difference lies in the fact that in the dog without a pancreas the catabolic factor of the carbohydrate metabolism is less strong, that of the fat and albumin metabolism more strong, while in genuine human diabetes the first is more strongly developed, and the latter factors fail almost entirely. Perhaps there may after all be elicited some grounds for the explanation of this considerable difference. On the one hand it might not be impossible that in the carnivorous dog the significance of the inner secretion of the pancreas is not quite the same for the metabolism as in the omnivorous human being.

We must then assume that in the dog the pancreatic hormone exercises also a direct inhibiting influence on the splitting up of albumin and fat. A certain decision of this question if exact observations of sudden and complete absence of pancreas [function] in man were at hand, which up to the present has not been the case.

On the other hand the following idea might very well be elicited from what has been said: *In experimental pancreatic diabetes, only the pancreas is absent, all the rest of the manifestations are secondary; in genuine human diabetes there exists, however, a disease of the whole apparatus regulating sugar metabolism (nervous centers in the medulla and brain stem, connecting paths, pancreas, and chromaffin tissue) with insufficiency, but not complete absence of one part and more or less independent hyperexcitability in the other part.*

Through this view, which has been the product of *v. Noorden's* clinic in recent years, the problem of the pathogenesis of diabetes mellitus has been broadened, but the solution of it seems only to have been thrust back one step further.

As far as the other glands are concerned in the bringing about of diabetic glycosuria, we may off-hand ascribe with certainty to only two other glands, the thyroid and the hypophysis, an important rôle in this direction. There exists, however, but little clearness in which way these ductless glands enter into the regulative mechanism of sugar metabolism, and whether they exercise this influence chiefly or exclusively by way of the pancreas. In the chapter on Basedow's disease we saw that hyperthyroidism was not rarely associated with a reduction of the assimilation limits for carbohydrates; indeed, that under circumstances, it could lead to spontaneous glycosuria. The circumstance that the alimentary factor is so prominent in these cases, speaks for the fact that through the hyperthyroidism there is called forth an insufficiency of the pancreas; further, the circumstance that with the suppression of the hyperthyroidism the glycosuria again disappears and eventually there come about normal relations, shows that this insufficiency is actually the result of hyperthyroidism. It appears therefore as has already been amplified in the chapter on Basedow's disease, that hyperthyroidism seems to signify a *functional* overloading of the pancreas; it is intelligible, from this standpoint, that glycosuria sets in only in individuals predisposed to it. As without such a functional overloading glycosuria would never occur, we are well justified in speaking of a *thyrogenic* glycosuria in such cases. This also is mostly easily delimited from true diabetes complicated with Basedow's disease.

As far as the diabetic glycosurias that occur so frequently in acromegaly and gigantism are concerned, it has already been set forth in the corresponding chapters that there is present in the great majority of cases an *organic* disease of the insular apparatus. It was mentioned there that in all conditions of hyperfunction of the glandular hypophysis a period of an abnormal tendency to growth is followed by a period of decay, and that the entrance of this decline is different in the various organs and especially in the various ductless glands. The insular apparatus appears to be especially sensitive. Besides these true diabetic glycosurias there is present in rare cases of acromegaly a similar condition to that observed in true thyrogenic glycosurias; there develops in these cases right at the beginning of the disease a glycosuria that later disappears and gives place to a normal assimilative ability. Whether this glycosuria is of thyrogenic origin or whether the hypophysis does not enter in some other manner directly into the regulatory mechanism of the carbohydrate metabolism, I shall not touch upon.

*v. Noorden* has portrayed the influence of the ductless glands upon the regulation of the carbohydrate metabolism in the following scheme. I have modified it that I have added to it two more connecting lines—one between the chromaffin tissue and the tissue at the periphery (chiefly the muscular system) and one between pancreas and tissue. This lends expression to the opinion that pancreas and chromaffin tissue directly regulate the assimilation and dissimilation of carbohydrates. Let it further be once again brought to attention that the line of connection between thyroid gland and pancreas is meant to express only the fact that increased thyroid activity disturbs the equilibrium to the disadvantage of the pancreas. Whether this happens through the influencing of the activity of the insular apparatus or through influencing the ultimate organs affected is still uncertain.

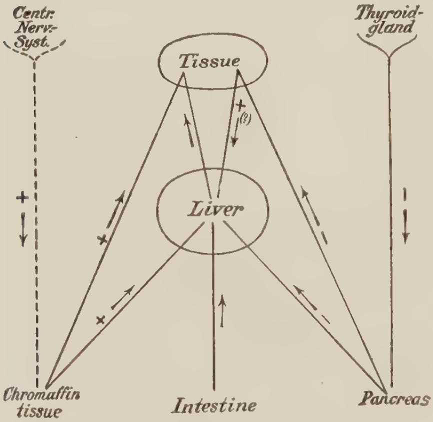

FIG. 95.

"The line of dashes represents nerve paths; the solid lines represent blood paths. The arrows show the direction of the excitation; the signs + or — behind them mean whether the stimulus transmitted by the respective path increases or diminishes the specific activity of the organ in question," whether it acts assimilatorily or dissimilatorily.

**Differential Diagnosis.**—A sharp separation of the ephemeral or transitory glycosurias from true diabetes is not practical. There are fleeting transitions between these forms. We would naturally not regard every individual who has one time eliminated grape-sugar in his urine as a diabetic; otherwise if investigations as to alimentary glycosuria (100 gm. grape-sugar) carried out at great intervals result always negatively, we could with justification speak of the cure of the diabetes.

We would think in general of a pancreatogenic diabetes when the alimentary factor comes strongly in the foreground; especially if pancreatogenic resorptive disturbances are present; further in all those conditions, which according to experience favor infection of the pancreas; hence in cholelithiasis, pancreatic stones, further in lues, cirrhosis of liver, and arteriosclerosis, etc. *Hirschfeld* regards also the behavior of diuresis as a differential diagnostic factor. It is not unlikely that in true pancreatic diabetes there is at the beginning no polyuria.

In glycosurias that occur during the course of infectious diseases, there is indeed much that speaks for the involvement of the pancreas in the infection; there is much for the thought, however, that the violent conditions of excitation in the vegetative nervous system may be of significance for the genesis of a nervous glycosuria.

For the assumption of a nervous glycosuria there are brought about symptoms that indicate a disease of the pons, cerebellum and medulla oblongata, perhaps also circumstances that can bring about an irritation of the splanchnics or the great sympathetic ganglia either directly or by circuitous routes; especially, then, severe neuralgias. Further we have to turn our especial attention to the behavior of the vegetative nervous system and the influencing of the glycosuria through the psyche. In many cases we can perhaps carry out the test for adrenalin glycosurias (in the aglycosuric condition) or *Löwi's* reaction; high-grade polyuria as well as simultaneously existing hypertonia speak for the nervous form or for a strong associated involvement of the nervous system.

Finally, concerning the thyrogenic form, naturally we must take pains to detect synchronous systems of hyperthyroidism. I would mention that in all the cases of true thyrogenic glycosuria that I have seen the eye symptoms were at most indicated. But tremor, sweats, and mononucleosis of the blood were always present. A higher degree of glycosuria speaks well against the purely thyrogenic origin. Simultaneously existing fat stools with strikingly good splitting of the fat and abundant soap-contents speak for the thyrogenic glycosuria. The diagnosis would be assured, if with the retrogression of the hyperthyroidism (spontaneously or by means of Röntgen illumination, etc.), the glycosuria disappeared altogether, and now also strong loading of the carbohydrate metabolism no longer led to elimination of sugar.

To close with some *therapeutic* points of view. In pancreatogenic diabetes the difficult feature of the treatment up to the present lies in the diet, which purposes to avoid [the functionating of] the diseased organ. This is brought about by limitation, or even by temporary complete withdrawal of the supply of carbohydrates and by simultaneous limitation of the supply of albumins. Also in cases with ketonuria there should be avoided an abundant supply of fat. The patient should be made free of sugar, and when possible, maintained sugar-free. There often occurs in such cases a restoration of the insular apparatus; if later then the investigation shows that the assimilatory ability has significantly increased, carbohydrates should again be administered at times in order to avoid permanent poverty in glycogen. The great significance of *v. Noorden's* oat-meal treatment lies in the fact that in an individual under-nourished with carbohydrates large quantities of glycogen are administered as an increment. Thus is often explained the wonderful action on the ketonuria. The catabolism becomes limited. In the severe forms the complete withdrawal of carbohydrates is not possible permanently, as the complete absence of glycogen increases the formation of ketone bodies entirely too markedly. Here we must try to restrict the glycosuria at least as much as possible, and counteract the overloading with acids by alkali therapy.

Much indeed speaks for the fact that in the nervous form too vigorous dietetic measures act unfavorably, although *v. Noorden* points out that in such cases a weakness of the insular apparatus may always be supposed, which tends to come to the fore in the further course, and therefore that a complete disregard for prophylactic dietary prescriptions may be disastrous for the patients. In the pure thyrogenic form the treatment of the hyperthyrosis occupies the foreground, in the pursual of which, however, vigilance in a diatetic respect is not excluded. The treatment of diabetes in acromegaly should coincide with that of the genuine diabetes.

## Addendum

*Allen,* in his book on "Glycosuria and Diabetes" draws an essential distinction between the two conditions, pointing out that in nondiabetic animals the limits of tolerance are apparent, not real, and that in these animals there is no real limit to the power of utilization of the sugar except death. Also that in the various forms of glycosuria dextrose always produces a limitation of the amount of urine, never a diuresis as in diabetes. He divides diabetes by pancreatic operation into a diabetes gravis and a diabetes levis, according to whether dextrose is or is not excreted on meat diet, and each of these into a permanent and a transient form. Permanent diabetes gravis and transient diabetes levis are absolute terms; but transient diabetes gravis and permanent diabetes levis are relative, the two conditions passing into each other. These various types depend on the condition of the pancreatic remnant. The ways that diabetes could be produced when the pancreas remnant is of more than ordinary size is by an irritative nervous lesion, such as the *Bernard* puncture and by circulatory disturbances in the pancreas. The fact that the nervous system can influence the pancreatic hormone, as is practically also *Falta's* conclusion, seems to the translator to speak in favor of *Crile's* contention that diabetes may be conditioned centrally, the nerve cells showing chromatolytic changes. At all events the intermediation of the islands of *Langerhans* of the pancreas remain unquestioned, this bringing about a deficiency of what *Allen* terms "pancreatic amboceptor." According to *Allen's* experiments there occurs in diabetes not a change in the hepatic cells that cause them no longer to fix dextrose, but a change in the physical state of dextrose itself. Instead of combining with a colloidal "pancreatic amboceptor" to be in a condition to be utilized, it maintains its ordinary crystalloidal properties, thus causing diuresis. Whether there is any distinction between pancreatic hormone and the pancreatic amboceptor does not seem very clear in a cursory review of *Allen's* voluminous work. *Allen* seems to call the substance an amboceptor because it acts as an intermediary body between the dextrose and various body cells. It has in common with hormones, at all events, the fact that it is an internal secretion, dependent on the integrity of the insular apparatus of the pancreas. Evidence is brought forward that at least one form of diabetes insipidus is associated with circulatory disturbances of the pancreas (how is this diabetes insipidus to be correlated with the polyuria approaching a diabetes insipidus that occurs in certain hypophysial affections?), but that is not associated, as is diabetes mellitus, with any evidence of insular involvement.

It is probable that the good effects of oats on diabetes are due to the fact that rest is provided for the pancreas. According to *Allen:* by reason of freedom from harmful stimuli from the intestine, also perhaps by reason of a diminished labor of external secretion, and possibly by reason of a mild beneficial stimulation in a positive sense, the pancreas is able to perform its function of internal secretion more efficiently, and the diabetic condition is correspondingly benefited. This explanation agrees with facts in the literature.

### REFERENCE

*Allen* (*F. M.*). Studies concerning glycosuria and diabetes. Boston, 1913, N. M. Leonard.

## CHAPTER XIV

# THE DIFFERENT FORMS OF OBESITY AND ADIPOSITAS DOLOROSA

We have already spoken of obesity in various chapters. It seems to me appropriate, however, to describe the relations of the ductless glands to the pathogenesis of obesity, even though I do not tell anything new. Further, it would be appropriate to discuss the relations between obesity and lipomatosis, as also the origin of lipomatosis has been brought into relation with disturbances of the ductless glandular system.

### A. THE DIFFERENT FORMS OF OBESITY

Two different principal types of obesity have been distinguished (*v. Noorden, Lorand*) *exogenous obesity* and *endogenous obesity*. By exogenous obesity *Lorand* understands the obesity of big eaters—that which later becomes combined with diabetes; endogenous obesity he refers to a disease of the ductless glandular system. Such individuals are for the most part anemic, it is an "unhealthy fat," and the combination of the disease condition with diabetes belongs to the great rarities. The separation and characterization of both forms has been carried on exhaustively by *v. Noorden* in his monograph on obesity.

According to *v. Noorden* exogenous obesity is either an overfeeding obesity or a laziness obesity, or the result of both factors combined. Exogenous obesity often occurs familially or hereditarily, although *v. Noorden* points out that in many of these cases there has been much more the hereditary transmission of a habit of living than that of a definite constitution. Naturally cases occur that must be regarded as transition forms between exogenous and endogenous obesity. A further entrance into the subject of exogenous obesity does not lie within the confines of my theme; I shall refer to the exhaustive exposition of *v. Noorden*.

In endogenous obesity much value has been laid on the demonstration of a diminution of the fundamental exchange and great pains have been taken in the demonstration. While such a diminution may be demonstrated in myxedema with certainty and ease, the attempts to demonstrate it in endogenous obesity have met with great difficulties. As the fat tissue only takes part in internal respiration to a limited degree, the fundamental exchange must fall very strongly in each fat individual if we wish to calculate it per kilo of body weight. But we possess no method of estimating the fat contents of an individual, but must rely on coarse, insufficient, estimations. The investigations up to the present on the fasting and rest values of corpulent individuals (*v. Noorden*, *Thiele* and *Nehring*, *Stüve*, *Magnus-Levy*, *Rubner*, *Jacquet* and *Svenson*, *Salomon*, *Reach*, *Staehelin* and *v. Bergmann*) have been subjected to an analytical criticism by *v. Noorden;* the calculation of the exchange per kilo of body weight, must, as already mentioned, be rejected as of no use. The calculation of the quotient $\frac{O_2 \text{ consumption}}{\text{body height}}$ shows in corpulent individuals higher values sooner than in normal individuals. This is perhaps due to the fact that in heavy accumulations of fat the work of the heart and of the respiratory muscles is perhaps made more difficult. *v. Noorden* arrived at the result that the estimation of the respiratory exchange at rest has up to the present furnished no sure decision in this question. This is true apparently of the estimations up to the present of the factors influencing the exogenous respiration gaseous exchange. Some one has expressed the opinion that in the corpulent the ingestion of food should call forth a slighter increase of the exchange. Herein lies a tendency to saving. The experiments that have been made up to the present, however, do not bear strict criticism. Up to the present only the determination of the calorie requirements has led to reliable results in some cases. The supply of heat was estimated in a very careful manner and for a long period, and it was determined that corpulent persons either take on fat or do not lose it under conditions under which normal persons either would not become corpulent or would lose in body weight. In this method care should be taken that exogenous factors are not allowed to take a part. The corpulent individual, to whom every movement is attended with exertion and is disagreeable, has often learned to get along with the minimum of movement, otherwise he sits and stands as a normal individual. To this must be added also the phlegm of such individuals. These methods can thus furnish a certain conclusion as to the diminution of the fundamental exchange, if extremely low values are found. This is actually the case in the cases reported. Such cases are, however, as *v. Noorden* has pointed out, quite rare.

We must now consider the question as to whether a diminution in the fundamental exchange characterizes endogenous obesity, and whether this is necessary for the assumption of a case as such. In a typical myxedema it is true that simultaneously with the reduction in the fundamental exchange there occurs an increase of the body weight, but not always, however, throughout as far as obesity. It is much more probable that the increase in weight can depend solely or in great part on the accumulation of myxedematous tissue and the water accumulation. In normal grown individuals the ingestion of food rises or falls with the greater or lesser need for it. The body weight, apart from slight variations, often remains the same for years at a time. This depends on a fine regulatory mechanism that as yet has not been investigated sufficiently. The most important element in the same is the appetite, although at times we eat very much more than the appetite really craves for, and then follows a period not of lessened appetite, but perhaps of increased demand for movement, the cause of which we do not know. May not, perhaps on the occasion of too great demand on the assimilation, substances arise which give occasion to this desire for movement? If now the diminution of the fundamental exchange increases the body weight, that is, the need for food does not keep pace with the exchange, it seems to me that a diminution of the fundamental exchange is less to blame for this increase in body weight than a disturbance of the regulatory mechanism; and it is perhaps not inconceivable that there are forms of endogenous obesity without diminution in the fundamental exchange. In exogenous obesity, according to this point of view, the regulatory mechanism is disturbed voluntarily or on account of bad habits (*v. Noorden*), in endogenous obesity, involuntarily through an alteration in the working together of the factors governing assimilation. If now I investigate how far such factors depend on the function of the ductless glands, it is known to me that I trespass into the territory of speculation, yet I see no other way of bringing into association the few certain observations that we possess on this question. At first I must again call to mind that the ductless glands exert an influence on both the endogenous and the exogenous factors of the total exchange. Upon the endogenous through diminution of the vegetative functions, for example; on the exogenous by their influence on the temperament, the psyche, the desire for movements, etc.

## 1. Pancreatogenic Obesity

I would tell in the first place about a form of obesity, whose genesis has yet not been furnished to us. It is observations from the physiology and pathology of metabolism that makes the supposition of such a form possible; if this supposition, however, suffices, many other forms of endogenous obesity may be made the more readily intelligible from this standpoint. The complete extirpation of the pancreas in the dog leads to an appreciable increase in the gaseous exchange. High-grade insufficiency of the insular apparatus in man is not, however, associated with an essential raising of the heat-production. Therefore, if although up to the present there has not been demonstrated by gaseous-exchange experiments concordant results as to a quenching of the heat production through the function of the insular apparatus, yet other considerations seem to ascribe to the pancreas an important rôle in the calorie economy.

*v. Noorden* first adhered to such an opinion, in that he indicated the possibility "that fixing of glycogen and sugar-production can be disturbed, while fat formation from carbohydrate still functionates. The fat tissue then takes up the excessively formed carbohydrate (as fat); there already exists a true diabetic disturbance of metabolism, but without glycosuria" (diabetogenic obesity).

I would see in the following consideration a further possibility.

It is known that carbohydrates have the ability to save albumin to a much larger extent than fat, and that an individual can hardly maintain his nutrition on albumin and fat alone. An abundant feeding, especially when there is a simultaneous raising of the protein constituent, succeeds only when there is abundant carbohydrate in the diet. Hence carbohydrate diminishes the decomposition of the albumin. As the specific dynamic energy of albumin is very much higher than that of fat and of carbohydrate the increase of the calorie production associated with the more abundant ingestion of nutrition is restricted. Now to-day there is not the particle of a doubt that the accumulation of carbohydrates is under the governing power of the insular apparatus. There must also accrue to the pancreas a direct influence on the assimilation of fat, not only because on the ingestion of abundant carbohydrates a portion of these is converted into fats, but because we see in severe diabetes the elimination of ketone bodies increase enormously on the administration of abundant fat. *For fattening, therefore, is necessary a functionally intact pancreas.* That we so often see diabetes supervene in fat people is perhaps due to the fact that the long overstrained pancreas becomes insufficient, apart from the circumstance that chronic overfeeding is often associated with other factors deleterious to the pancreas (alcoholism, continual hyperemia of the abdominal organs, etc.).

The considerations up to the present are concerned chiefly with exogenous obesity. We can conceive, however, that the origin of obesity may receive an impetus through a *primarily strengthened function of the insular apparatus*, in that the assimilation of larger amounts of food goes on abnormally easily, and that by this does not occur the setting free of those reactions which in normal individuals work against an ingestion of food that for a long time supersedes the need.

## 2. Thyrogenic Obesity

The idea of thyrogenic obesity was first set forth by *von Hertoghe*, *v. Noorden*, *Lorand*, *Ewald* and *others*. Occasion for it was given by observations of rather rapidly developing obesity with slight symptoms of hypothyrosis, slight puffiness of the face, apathy, diminution of memory, insomnia, etc. To it is often added a slight grade of anemia. Such individuals often bear reducing treatment very badly. *v. Noorden* mentions especially that in such cases reducing treatment often leads to conditions of cardiac weakness, while a thyroid-gland treatment is often accompanied by rapid result, the manifold oppressive symptoms disappear, the individuals become livelier, fresher, and although they eat with appetite and do not essentially restrict the intake of food, they now gain in weight rapidly. There appear to be very different etiological factions that lead to such a slight functional disturbance of the thyroid gland. In many cases there had been numerous confinements following each other at short intervals. In others the obesity develops immediately at the close of a protracted infectious disease. *v. Noorden* mentions for example cases in which the obesity developed progressively after an abdominal typhoid, and refers to similar examples from the French literature.

The diagnosis of this form of obesity is often difficult, because the symptoms of hypothyrosis are only suggested. The justification for one's regarding the hypothyroidism as the cause of the obesity, can, however, in many such cases indeed not be doubted. It is found in the entire course of the disease and in the excellent action of the thyroid treatment, which we may regard as a sort of functional test. Of course thyroid gland acts as an agent that reduces weight also in the cases of ordinary exogenous obesity. The essential point lies, however, as *v. Noorden* mentions, in the difference between the complete action of the thyroid cure and the intolerance against much withdrawal of food, and, as I would attach especial value to, in the high tolerance for thyroid-gland preparations. From the theoretical standpoint the assumption of such a thyrogenic obesity is well founded. We can conceive that just in such slight degrees of thyroid-gland insufficiency, the balance between thyroid-gland function and the function of the pancreas is disturbed in favor of the latter, and that thus is furnished the impulse for the origin of an obesity, while with a severe disturbance of the function of the thyroid often all vegetative functions are highly diminished, and therewith the ingestion of food and the appetite are restricted. The very general observation that in such cases of thyrogenic obesity the assimilation limits for carbohydrates lie abnormally high, indicates with the greatest probability a preponderance of the pancreatic function.

### 3. Dystrophia Adiposo-genitalis

In this form, whether it be of primary genital or hypophysial origin, there is found a characteristic distribution of fat such as has been described in detail in the corresponding chapters. It depends on the withdrawal or the weakening of the protective influence of the interstitial glands on body formation. The distribution of fat has per se nothing to do with obesity, as it is retained in such individuals when they otherwise become very thin on any other basis, and for the reason that sure cases of hypophysial dystrophy and also many eunuchoids do not come to the development of a pronounced obesity, while the abnormal distribution of fat is always present. Also a certain degree of fatty infiltration of the muscles may be peculiar to this dystrophy, independently of obesity, as well as a weak, velvety texture of the skin, and the behavior of the hair. The fact is, however, that in both forms, obesity develops very commonly, even to excessive degree. The factors that give occasion to this are as yet not entirely clear. We must consider that eunuchoids have another temperament than normal individuals; they are less lively, have less energy, the muscular tonus is slighter; in hypophysial dystrophy there also happens that in the severer cases the vegetative functions apparently course more slowly, and the fundamental exchange therefore is established at a low level, as indeed the experimental investigations on animals have shown. Also in these forms does the function of the insular apparatus seem to have a certain preponderance, at least, as has already been set forth in detail, in almost all cases has a strikingly high tolerance for carbohydrates been found. In the intimate pathological correlations between glandular hypophysis and thyroid, also a thyrogenic factor can, in many cases of hypophysial dystrophy, very well play a part. Ordinarily this does not seem the case, at least the result of a thyroid treatment in such cases is not so excellent as in the ordinary obese individuals, and the tolerance for the administration of thyroid gland is not essentially higher. There are numerous statements in the literature that in such cases of hypophysial dystrophy the peroral administration of hypophysis tablets or eventually a combination [of these] with sexual gland substance was followed by results.

### 4. Epiphysial Obesity

It is as yet doubtful whether we are justified in setting forth such a form. At all events it is remarkable that commonly with the development of pineal tumors in adults, obesity also develops. Then again this may attain an excessive degree. It can readily be conceived that the obesity may be brought about on account of limitation of function of the neighboring hypophysis. Actually in the case of *Raymond* and *Claude* the hypophysis was very much flattened. One would then expect the other characteristic symptoms of hypophysial dystrophy in all cases. From the cases in the literature, which, however, have not been described very exactly, I have not succeeded in eliciting a safe basis for this.

## B. ADIPOSITAS DOLOROSA

In the years 1882 and 1892 respectively, *Dercum* described a disease picture which is characterized by the peculiar form of fattening and by the painfulness of the fat masses. Later *Vitaut* called attention to two additional cardinal symptoms, namely the asthenia and certain psychical alterations. *Dercum* saw the cause of this disease in an especial form of dysthroidia; since that time numerous appropriate cases have been reported; the most authors adhere to the ductless glandular pathogenesis of this disease, although others, especially French authors, oppose the setting up of this syndrome as a disease sui generis, in that they advocate the opinion that from this syndrome transitions go over to the different forms of lipomatosis and to the trophic edemas. Lately *Lyon* is even of the opinion that also the different forms of obesity and those of lipomatosis go over into each other without sharp boundaries. Many authors assume a nervous trophic origin for this syndrome. Before I enter into the description of the syndrome, I would like to report an appropriate case.

*Observation LXX.*—Fr. B., fifty-six years old. Entered the first medical clinic Sept. 3, 1912. The parents of the patient were both corpulent. Of five brothers three are very corpulent, and of four sisters, two. According to the statement of the son the localization of the fat in the corpulent relatives is not just the same as in the patient. The four children are not adipose. There is no diabetes or gout in the family, so far as is known. As a child and youth the patient was healthy. The obesity began to develop during the military service, especially later, however, when the patient adapted a sedentary life; he was landlord of an inn and ate and drank very much, consuming 4½ liters of wine daily and smoking very much. The obesity was especially heavy from the thirty-fifth year of life on. The fat developed in cushions on the shoulders, on the upper arm, on the thorax, and on the pelvic girdle, while forearms and hands and [lower] legs and feet remained thin. For about ten years there often occurred oppressions of respiration and vertigo, especially on going up stairs and on long marches. Lately he can hardly walk on this account. The appetite became slight, and he ingests practically only liquid nutrition. In the spring of 1912 he weighed as much as 140 kg. Since that time he lost about 30 kg. For a long time there has existed pains in the hepatic region; during the last weeks he vomited several times daily, independently of the ingestion of food, also belches. For the last year there has

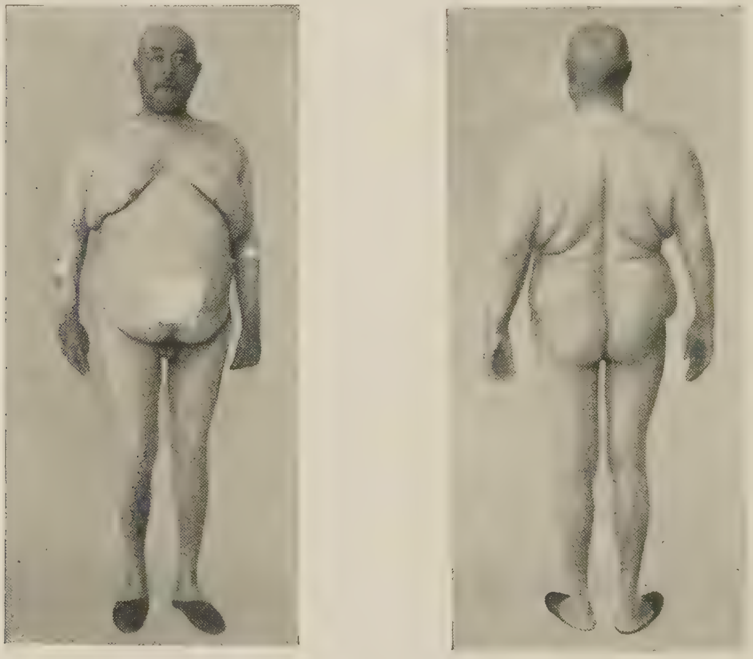

FIG. 96.—Case of adipositas dolorosa (Observation LXX).

been entire impotence and failure of libido which for a long time has been developed only very moderately.

The patient now weighs 105 kg. and by Nov. 9 had lost 3 kg. more. The body length is 170 cm., the span width, 169 cm., the greatest circumference of the abdomen, 124 cm. There are enormous accumulations of fat on the upper arms and on the outer sides of the shoulders, also on the inner side of the upper arm, also a thick cushion of fat over the vertebra prominens (a true fat neck), also on the outer sides of the buttocks and of the thighs; the thin forearms and [lower] legs stand in characteristic contrast to the heavy fat accumulations on the shoulder and pelvic girdle. In consequence of these the patient presents the appearance of an athlete. On closer examination, however, it is noted that the body build is slender, and that thorax and pelvic girdle are not abnormally broad. The circumference about the shoulders is, in consequence of the enormous cushions of fat, 128 cm. The circumference of the abdomen a hand's breadth under the xiphoid process is 122 cm., the greatest circumference of the thorax, 123 cm., the greatest circumference of the upper arm on both sides, 40 cm. On the inner side of the forearm may be felt on both sides several symmetrical fat nodules, the size of a nut; the fat has accumulated more abundantly on the upper part of the thorax, in the vicinity of the nipples, so that it drapes forward in two enormous folds, directed obliquely outward and downward, and drapes backward in several oblique and horizontal folds. From the waist on the fat again begins to be enormous, so that it hangs below like an apron over the symphysis and half conceals the genitalia.

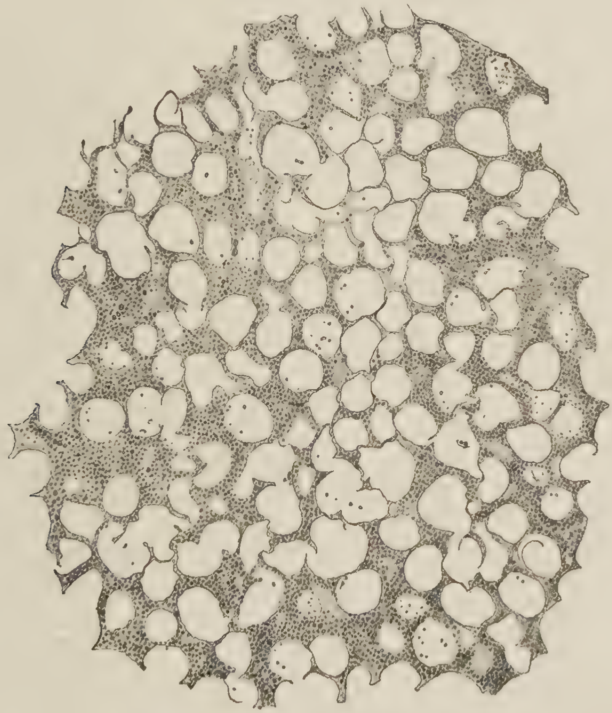

FIG. 97.—Inflammatory alteration of the feet-tissue in a case of adipositas dolorosa (Observation LXX.)

Also laterally over both iliac bones are enormous fat nodules that are bounded below by folds. On the outer side of the femur palpation reveals a more diffuse embedding of dense nodular fat. On the inner side is found on each side an enormous fat nodule. The distribution of fat is everywhere strictly symmetrical. At some places are found thick symmetrically disposed fat nodules of the size of a hen's egg to that of an apple. Often the nodules are smaller, seeming to the palpating finger like small nodules. Everywhere over the fat cushions are to be seen ectasic veins, around which are plainly evident in the whole course of the veins fat disposed like bunches of grapes. Here the fat is especially painful.

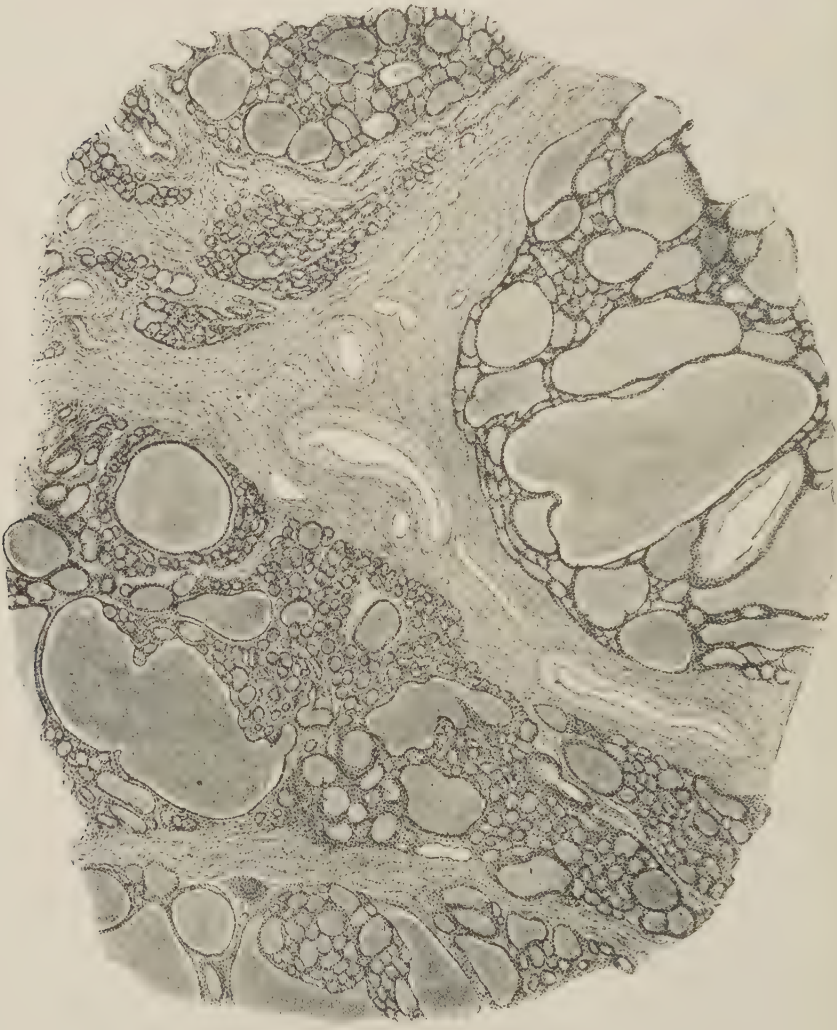

FIG. 98.—Thyroid in a case of adepositas dolorosa (Observation LXX).

The left lobe of the thyroid gland shows a struma about the size of a goose egg.

The border of the liver is palpable three finger-breadths below the border of the ribs, and is hard. The urine shows urobilin and traces of albumin.

Test as to alimentary glycosuria (100 gm. dextrose) negative.

After injection of 3 cc. pituitrinum glandulare, and later 5 cc., there was no increase of temperature.

The blood sugar-contents is normal.

Blood count: Leucocytes, 12,000, of which:

Neutrophiles, 50 per cent.

Lymphocytes, 42 per cent.

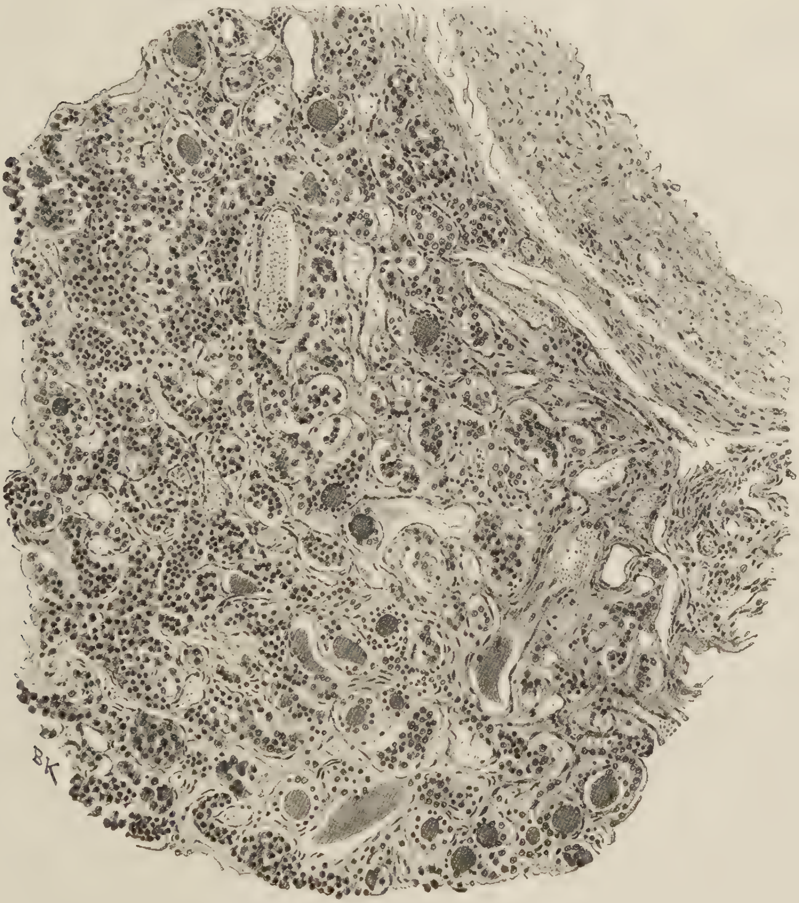

FIG. 99.—Hypophysis in a case of adipositas dolorosa.

Large mononuclears, 6 per cent.

Eosinophiles, 2 per cent.

X-ray shows that the aorta is 7 cm., the heart 13.5 cm. broad. The genitals show nothing especial.

The sella turcica is seen (by X-ray) to be of normal size.

Nerve status. The fundus is normal. The pupils react promptly. Patellar reflexes are weak on both sides, superficial abdominal and cremasteric reflexes normal. No Babinski, no Romberg. Slight paresis of the right facial nerve. Distinct alcoholic tremor. Gross strength of the muscles reduced. Gait somewhat insecure. Sensibility not essentially disturbed.

The microscopical examination of an excised piece of fat showed pronounced perivascular infiltration consisting especially of mononuclear, and partially of polynuclear cells. Especially distinct is this infiltration in the interstitial connective tissue between the individual fat lobules, although the smallest perivascular infiltrations are found also around the capillaries between the fat cells themselves.

The patient went down very rapidly, soon he was not oriented any more as to time and space; there occurred hallucinations of faces, he spoke confusedly, believed himself to be on a journey, whistled and made a noise, especially at night. Apparently there was diplopia on looking toward the left. Slight paresis of the left abducens. The ingestion of food became always slighter; nutritive enemas were not retained. At times vomiting. The pulse accelerated, small, soft cardiac remedies were without effect. At the close there developed an ulcerous pharyngitis, later bronchitic murmurs; death occurred with increased cardiac weakness.

Autopsy (Assistant Dr. *Schopper*). Hypertrophic cirrhosis of the liver with moderate enlargement of the organ and uniformly granulated superficial and cut surface. Marked fat infiltration of the heart in the form of nodular fat lobules with penetration of the fat until into the endocardium. Concretio cardio cum pericardio. Increase of the fat also in the pericardium, hypostasis of the lungs, etc. Chronic internal hydrocephalus with granular thickening of the ependyma. Slight fatty degeneration of the kidneys and of the myocardium. Acute splenic tumor. Ulcerative pharyngitis. Marked atheromatosis of the aorta. Slight sclerosis of the peripheral arteries.

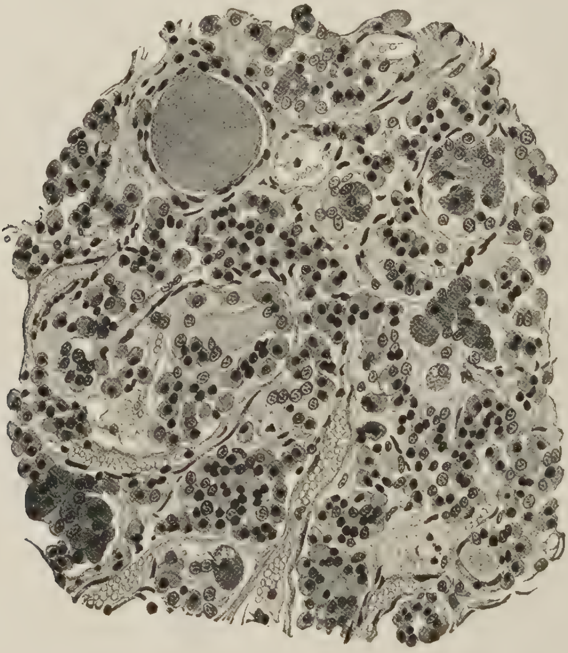

Fig. 100.—Anterior lobe of hypophysis in a case of adipositas dolorosa (Observation LXX).

The distribution of fat corresponds to the clinical description. The fat is of a yellowish gray color, firm consistence with individual stripes and spots of white-grey color that are appreciable even macroscopically.

The hypophysis is rather small, otherwise macroscopically normal.

The thyroid gland is macroscopically for greatest part quite normal, in the left lobe is found a goose-egg-sized strumous nodule.

The suprarenals are microscopically normal.

Also in the sexual glands is found nothing especial. The pancreas is macroscopically normal.

The microscopical examination of the pancreas and the suprarenals showed fully normal conditions. The microscopical examination of the thyroid gland showed, as the adjoining illustration shows, a colloid struma, yet there is still found everywhere abundant thyroid glandular tissue of normal consistency (Fig. 98).

Also the microscopical examination of the hypophysis showed normal relations, as well in the glandular lobe as in the nervous lobe and in the pars intermedia.

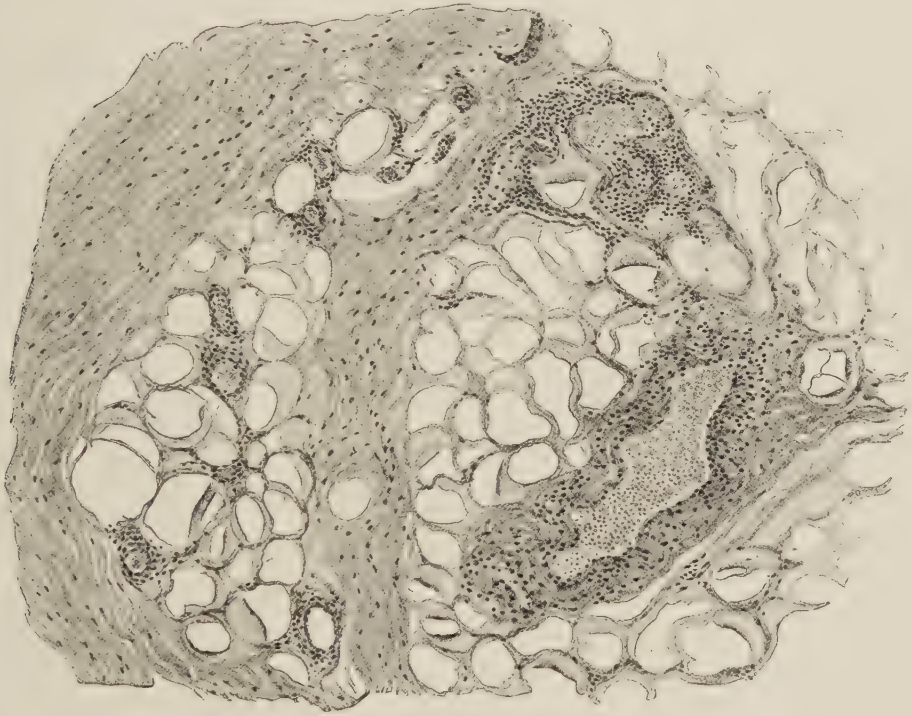

FIG. 101.—Perivascular infiltration in a case of adipositas dolorosa (Observation LXX).

Fig. 99 shows a general view.

Fig. 100 shows a portion of the glandular part on higher magnification.

Also another piece of fat tissue was examined microscopically; in this section there was a perivascular infiltration, more distinctly developed about the large vessels. See Fig. 101.

**Symptomatology.**—Adipositas dolorosa or adiposis dolorosa is found more commonly in women than in men. It usually begins between the forty-fifth and the sixtieth years of life. In women the disease often sets in with the menopause. There are, however, individual cases in which the beginning occurred at the eleventh year of life. As cardinal symptoms of the disease are regarded, the fat tumors, the tenderness of the fat to pressure or its painfulness spontaneously (*Dercum*), the asthenic and the psychical alterations

(*Vitaut*). In addition there have been described, however, a series of accessory symptoms, that consist especially in disturbances on the part of the motor, sensory, and vegetative nerves.

The distribution of the fat tumors may be very different. *Vitaut* first distinguished:

a. Nodular, asymmetrical fat tumors, disposed asymmetrically in and under the skin—lipomatose nodulaire.

b. Uncircumscribed, diffuse, sharply delimitable fat growths, lipomatose diffuse localisée.

c. General diffuse fat growths, lipomatose diffuse générale; this is the most frequent form, and in it the fat is not uniformly distributed as in ordinary adiposity, the skin shows much more an uneven texture. The fat masses feel lump-like, like a bundle of worms (*Dercum*), and at those places especially where a pressure is exerted, for instance in the waist, or where the garters press, they are separated from each other by deep furrows.

In lipomatose diffuse localisée the accumulations of fat are mostly found only on the trunk and on the proximal third of the extremities. In such cases the fat deposits may be quite excessive and hang down like an apron, as for instance in a case of *Dercum* and *McCarthy's*, in which the fat masses hung laterally over the hips and backward over the buttocks in thick folds, or in a case of *Löning* and *Fuss's* in which the fat masses hung from the abdomen and the inguinal region almost to the lower third of the thigh.

In the nodular form the throat and face, as well as hands and feet, eventually also the forearms and [lower] legs are entirely free; the latter are often very thin. In a case of *Debove's* there was found, especially on the outer side of the upper arm, symmetrically disposed masses up to the size of a pigeon's egg. The hands were entirely free. These fat nodules may be arranged in a multiple manner, or symmetrically.

On careful observation of the reported cases we may see that all transitions between these three types occur. This was already observed by *Weiss;* the classification has but little value. I refer to the case detailed above, which constitutes a combination of lipomatosis nodulaire and lipomatosis diffuse localisée.

The second cardinal symptom consists in the painfulness of the fat. In many cases there is a sensation of violent burning "as if a dog were tearing the flesh from the body" (*Haškovec*) in other cases the pains occur in attacks, under circumstances before the fat infiltrates become visible. In other case vesicles appear during the attacks of pain. In other cases spontaneous pains are absent, the fat infiltrates are painful only on pressure; in my case the painfulness of the fat infiltrate was bound chiefly to the vicinity of the dilated veins. There are also cases described, otherwise typical, in which the tenderness to pressure was but very slight.

In all cases the asthenia is more or less distinctly pronounced. In the case described above, the muscular weakness was so great that the patient could scarcely walk.

Psychical alterations are indeed very common, but not constant. The case of *Löning* and *Fuss*, a sixty-six-year old woman in whom the disease had existed for about twelve years was mentally entirely normal and active. The psychical alterations are very various. In many cases hallucinations and conditions of excitement are observed, in others, as for instance *Ballet's* case, depressive melancholic conditions. Also the accessory symptoms are very diverse and not constant. On the part of the motor nerves are observed tremor (alcoholism), slowing of the speech, alterations of the reflexes, especially reduction. On the part of the sensory nerves are stated hyperesthesias and paresthesias, disturbances of the sensibility, etc., on the part of the vegetative nerves often vasomotor symptoms such as dermographism, also tachycardia, dyspnea, anidroses, hyperidrosis. In addition trophic disturbances, such as premature turning gray of the hair, and on the part of the vascular system hemorrhages, inclination to nose-bleed, purpura, etc. As may be seen, very diverse symptoms are collected together in this group. As we are mostly dealing with elderly people with fatty heart and severe alcoholism, many of these symptoms are readily intelligible without anything further.

Investigations as to the metabolism are as yet very sparse. *Schwenckenbecher* observed two cases in which the body weight only began to fall, when the administration of calories was as low as 19 calories per kilogram. In many cases polydipsia is asserted, in others reduction of the body temperature.

**Pathological Anatomy.**—There are already a series of autopsies, into a consideration of which I shall enter somewhat exactly as it is necessary for the discussion of the pathogenesis.

*Dercum* described two cases, in which were found macroscopically enlargement and calcareous infiltration of the thyroid gland. In a case of *Dercum's* was found uniform atrophy of the thyroid gland and widespread interstitial neuritis of the peripheral nerves in the depositions of fat. In a case of *Burr's* was found degenerative alterations in many lobules of the thyroid gland, also a glioma of the hypophysis, and in addition interstitial neuritis, sclerosis of the liver, and atrophy of the ovaries. In a case of *Dercum* and *McCarthy's* the thyroid gland was normal, there was found an adenocarcinoma of the hypophysis, enlargement of the right suprarenal, hemolymph glands in the fat tissue, interstitial neuritis, hypoplasia of the testicles, and acute parenchymatous nephritis. In a case of *Guillain* and *Alquier's* the thyroid gland was found to be enlarged and the connective tissue in it increased. The hypophysis was likewise enlarged, the connective tissue in the glandular portion was increased, in association with which the eosinophilic and basophilic cells were increased, alterations that reminded both these authors of an alveolar carcinoma. In a case of *Price's* there were found inflammatory alterations in the thyroid gland as well as in the hypophysis (alveolar or glandular carcinoma?) and interstitial neuritis. In a second case there was found in the thyroid gland much interstitial tissue, the acini were dilated, the hypophysis showed similar but not essential alterations. In the fat tissue were found no especial alterations. In a case of *Löning* and *Fuss's* the thyroid gland was dense, changed into a whitish-yellow callous tissue; microscopically was found smallness of the gland cells and round-cell infiltrate, the hypophysis was small, soft, unaltered. Finally, in *my* case there were no essential alterations in the ductless glands. We can hardly ascribe any especial significance to the colloid struma, there were found perivascular infiltrates in the fat tissue, and cirrhosis of the liver.

Summing up the autopsy findings we find the following: Among eleven cases, there were found nine times alterations of the thyroid gland, especially of a chronic inflammatory nature. The hypophysis was examined microscopically in seven cases. Among these were found alterations five times, and these indeed of a very diverse nature (round-cell infiltration, sclerosis, adenocarcinoma, glioma). Also in the sexual glands was sometimes found sclerosis, in addition to which was found ovarian cysts, and once hypoplasia of the testicles. Liver and spleen often show cirrhotic changes, the kidneys sometimes interstitial changes. The microscopical examination of the fat often showed, as well in the diffusely distributed fat as in the encapsulated lipomata, abundant connective tissue; and in some cases newly formed hemolymph nodules or perivascular inflammatory infiltration. In other cases there were chiefly found no inflammatory alterations. Very frequently, there was found interstitial neuritis (six times among seven cases investigated), as well in the fine nerve trunks in the fat tissue itself, as in the nerves of the muscles. In one case was found degeneration of *Goll's* column.

**Pathogenesis.**—The views of the authors as to the pathogenesis of adipositas dolorosa are very different. *Dercum* considered the cause of the affection as a sort of dysthyroidia, through which came about a reduction of fat combustion and inflammatory alterations of the nerves. *Vitaut* expresses himself similarly. Most of the authors assume a chronic intoxication, the cause of which they see in a disturbance of the function of the ductless glands (*Price*, *Ballet*, *Miquel*); but they are not agreed as to which ductless gland is at fault. For example, *Price* believes that in addition to the thyroid, the hypophysis plays an especial part, *Ballet* regards the involvement of the thyroid gland as unlikely and thinks of disturbances of the other ductless glands, etc. *Debove* places first the nervous system as the central figure of the pathogenesis. *Strübing* and *Thimm* regard the disease as a trophoneurosis, *Haškovec* as a central trophoneurosis. *Sicard* and *Roussky* think of an involvement of the ovary, as they saw the disease develop after ovariotomy in two relatively youthful cases. *Schwenkenbecher* believes in an endogenous obesity, the fat growth should press on the small vessels and nerves, causing circumscribed circulatory disturbances and paresthesias. We thus see that the views as to the pathogenesis of this disease diverge greatly.

Before I discuss the significance of the ductless glandular system for this disease, I would like to say a few words concerning the relationship of these to lipomatosis. The view has been adopted by French and German authors that adiposis dolorosa is no disease sui generis, but only a syndrome that belongs to the great group of lipomatoses and of trophedema. To my knowledge, *Köttnitz* was the first to point out that in the symmetrical lipomata there frequently occur constitutional symptoms, such as nervous symptoms, rheumatoid pains, etc. He describes a case, in which the menopause set in prematurely, and at the time of the failing menses, symmetrical lipomata several times developed, the eruption of which was attended with pain in the part of the body in question. Already *Köttnitz* holds adipositas dolorosa as a trophoneurosis and believes that all transitions to the painful symmetrical lipomata occur. Also *Cheinisse* and *Fulconis* maintain the identity of the two diseases. After *Potain* and *Mathieu* had assumed transitions from neuropathic edemas to pseudolipomata and even to true lipomata, especially *Strübing*, and after him *Thimm*, advocated the view that neuropathic edema (oedème blanc and bleu), multiple lipomatoses, symmetrical diffuse lipomata and finally the painful lipomata all belonged to a great group of diseases that "had at their foundation the same basic process." Also *Miquel* sought to establish in detail that the oedème neuropathique of *Mathieu*, the oèdeme segmentaire of *Debove*, the chronic trophedema of *Meige* and the pseudooedème catatonique of *Dide* formed with adipositas dolorosa a great group, the cause of which was to be sought in alterations of the nervous system and of the ductless glands. Lately *Lyon* after a careful compilation of the literature and the addition of new material, has advocated a similar view.

The view that fleeting transitions exist between painful symmetrical lipomata and adiposis dolorosa has received much support from the works of the last years. Already among the circumscribed lipomata that are often distributed in great number over the entire body are those, as *Launois* and *Bensaude* point out, that are painful to pressure and are associated with spontaneous neuralgiform pains. In the symmetrical lipomata the constitutional factor mostly comes still more strongly into the foreground. Here are frequently found manifestations of asthenia, also vasomotor disturbances, especially bluish-red coloration of the skin over the nodes, paresthesias, even psychic disturbances. Also in such cases the hereditary and familial element is often well pronounced. As an example I cite a case of *Lyon* (case 2). In two sisters painful symmetrical lipomata set in at the time of puberty and attained their full development at maturity. They were associated with rheumatoid pains, dysmenorrhea, and psychic impairment. According to *Lyon* there may be also found in such lipomata lymph nodules similar to those which are found in adipositas dolorosa. That in adipositas dolorosa the distribution of fat may be rigidly symmetrical is shown by the case quoted in detail above. A quite similar distribution of fat was found in a case of *Dercum* and *McCarthy's*. In my case, there were, in addition, lipomata up to the size of a goose egg, disposed rigidly symmetrical. This type of fat distribution was also present in a case of *Bochroch's*.

I will not venture to pass judgment on the question whether there are also transitions between lipomatosis and trophedema. I shall only register some important findings. In a case of trophedema, *Strübing* found on microscopical examination, no edema at all, but only fat with strikingly large fat cells. *Haškovec* describes a case in which there set in at the menopause pains in the back and in the limbs, attacks of weakness, and then edema, which, recurring constantly, closed with attacks of violent pains. At the site of the edema there then gradually developed a painful hyperplasia of the subcutaneous fat tissue. *Haškovec* regards this case as a transition of a vasomotor neurosis or an acute edema to a trophoneurosis. We must remember, however, that the acute edema usually shows quite another localization from that of the symmetrical lipomata. Also combination of adiposis dolorosa with other diseases that are regarded as trophoneuroses, for example, xanthelasma, are known. *Debove* has described such a case.

Finally, as far as the ductless glands are concerned in the pathogenesis of adiposis dolorosa, this seems to me very doubtful. The pathologico-anatomical alterations in the ductless glands are very diverse. As we have previously seen, there have been found rather frequently degenerative changes and especially chronic inflammatory changes in some of the ductless glands, especially in the thyroid gland and in the hypophysis. (The findings of adenocarcinoma or glioma of the hypophysis might very well be an accidental coincidence.)

These chronic inflammatory alterations seem to me throughout not remarkable, as in this disease we find them otherwise in many organs. Cirrhotic alterations in the liver and spleen, chronic inflammations in the nerves, etc., belong to the commonest findings, and may in part be explained by the alcoholism that is present. Thyrogenic obesity, a mild form of myxedema, is widely distinguished in its clinical behavior from the picture of adiposis dolorosa. Simultaneous sclerosis of the thyroid gland and of the hypophysis leads to a combination of myxedema and cachexia, a disease picture that has nothing to do with adipositas dolorosa. There does not appear to me to be any grounds for assuming the involvement of any of the other ductless glands. The assumption of *Lyon* that all forms of obesity and of lipomatosis have their origin in a disturbance of correlation of the ductless glands, I cannot subscribe to. Here too many things are thrown together. The supposition of the disturbance of correlation of the ductless glands as the cause of a disease, is, without corresponding pathologico-anatomical correlate a vague idea, that only obstructs a deeper penetration into the pathogenesis of such a disease. So that there remains at hand only the supposition of a trophoneurosis, although I cannot conceal the fact that not much has been gained by this assumption.

There have been described still other trophic disturbances of the fat tissue of which I shall here briefly refer to one only, although probably it has less to do with the ductless glandular system than adipositas dolorosa. *Pic* and *Gardère* first pointed out a trophic disturbance which *Simons* has lately designated lipodystrophia progressiva. It is concerned with disappearance of the fat on the face and arms, simultaneously with a gradually increasing adiposity in the region of the buttocks and on the thigh. Sensory and vasomotor disturbances are absent. The investigation of the fundamental exchange in *Simons's* case showed normal relations.

In the **differential diagnosis** of adipositas dolorosa from myxedema it must be considered that in the latter especially swellings in the face are present; from trophedema that this mostly sets in at an early age, that the edema is mostly unilateral and that hands, feet, forearms and [lower] legs are usually involved; from neurofibromatosis of *Recklinghausen* that the nodules are in this affection much harder and also smaller, that they are more confluent, that they do not avoid hands and feet, and that the psychic disturbances are more pronounced, also that there are often marked pigmentations of the skin (*Debove*). The differential diagnosis from alcoholic polyneuritis in the obese, concerning which diagnosis *Umber* and *Schwenkenbecker* have written, is often very difficult, if the characteristic distribution of fat is absent.

In the **treatment** of adipositas dolorosa a great rôle is played by thyroidin. In many cases the results are indeed undoubted, but this does not furnish evidence for the thyrogenic nature of the disease. It has been stated that cases have been cured by thyroidin medication (*Price*). Also the psychic disturbances have retrogressed. *v. Noorden* has seen good results from systematic bath-treatments. X-ray irradiation and iodine have been recommended.

## Addendum

The type of obesity described by *Anders* under the name adiposis tuberosa simplex is apparently nothing more than a transitional stage between simple diffuse obesity and adipositas dolorosa. It is doubtful whether even the latter will long maintain its position as a disease sui generis. It is probable that many of the cases described under it could very well be classed under the other varieties of obesity. In adipositas dolorosa we have the additional factor of pain, which may very well be explained as a neuritis of the small nerve filaments. In many of the histories there is quite enough to account for the existence of such a neuritis and also the mental changes; nor is the asthenia of sufficient importance to delimit this condition as a pathogenic entity, although for clinical purposes adiposis dolorosa does constitute one of the recognizable types of obesity.

This being the case, the question as to which ductless glands are at fault in adiposis dolorosa seems to me entirely misplaced. We may very well conceive that certain of the cases might (just as ordinary obesity) show no changes in the ductless glands at all, and that others might show changes in individual glands or in several, as in the varying types of obesity in general. In no case, or perhaps only very rarely, is the condition to be regarded as pluriglandular in the author's conception of the term, but rather as a result of a pathological or a physiological correlation.

*Price* has recently contributed a case that suggests to him the possibility that, in addition to the thyroid condition, there were some disturbances in function of the parathyroids—the woman showed alternating, long periods of apparent hypothyroidism and hyperthyroidism (without exophthalmus) and in addition, during or just before the periods of hyperthyroidism flexor cramps of the extremities, especially of the hands and the feet. Whether in this case these cramps would be considered a sign of hyperexcitability of the nerves such as would presage tetany, or constitute an attack of tetany, cannot be decided from the case report alone.

*McCarthy* and *Karsner* have recently reported a case of adenocarcinoma of the thyroid, with metastases to the cervical glands and pituitary, which they regard as linking together three of the groups of pathological fat—adiposis cerebralis, symmetrical adenolipomatosis (à prédominence cervicale) of *Launois* and *Bensaude*, and adiposis dolorosa. *McCarthy* regards another case reported by him with *Dercum* as an intermediate type between adiposis dolorosa and adenolipomatose symmetrique à prédominance cervicale. A third case mentioned by *McCarthy* in the report was evidently a case of eunuchoidism.

In the treatment mention should be made of the various "degrassators" that bring about a reduction of the fat by electrical means, also of hot steam or electrical light baths. It is needless to state that these measures should be employed in those weakened and debilitated individuals affected with adiposis dolorosa only with extreme caution, if at all.

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# LITERATURE

## CHAPTER I

### GENERAL PART

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# CHAPTER II

## THYROID GLAND

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# CHAPTER IV

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# CHAPTER V

## THYMUS

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# CHAPTER VI

## HYPOPHYSIS

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# CHAPTER VIII

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# CHAPTER IX

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# CHAPTER X

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# CHAPTER XII

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# CHAPTER XIII

## PANCREAS

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# CHAPTER XIV

## OBESITY

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